

Hígado

Patología Hepática No-Tumoral y Tumoral

Curso Pregrado, 4to año

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Patología Hepática, Gastrointestinal y Ginecológica

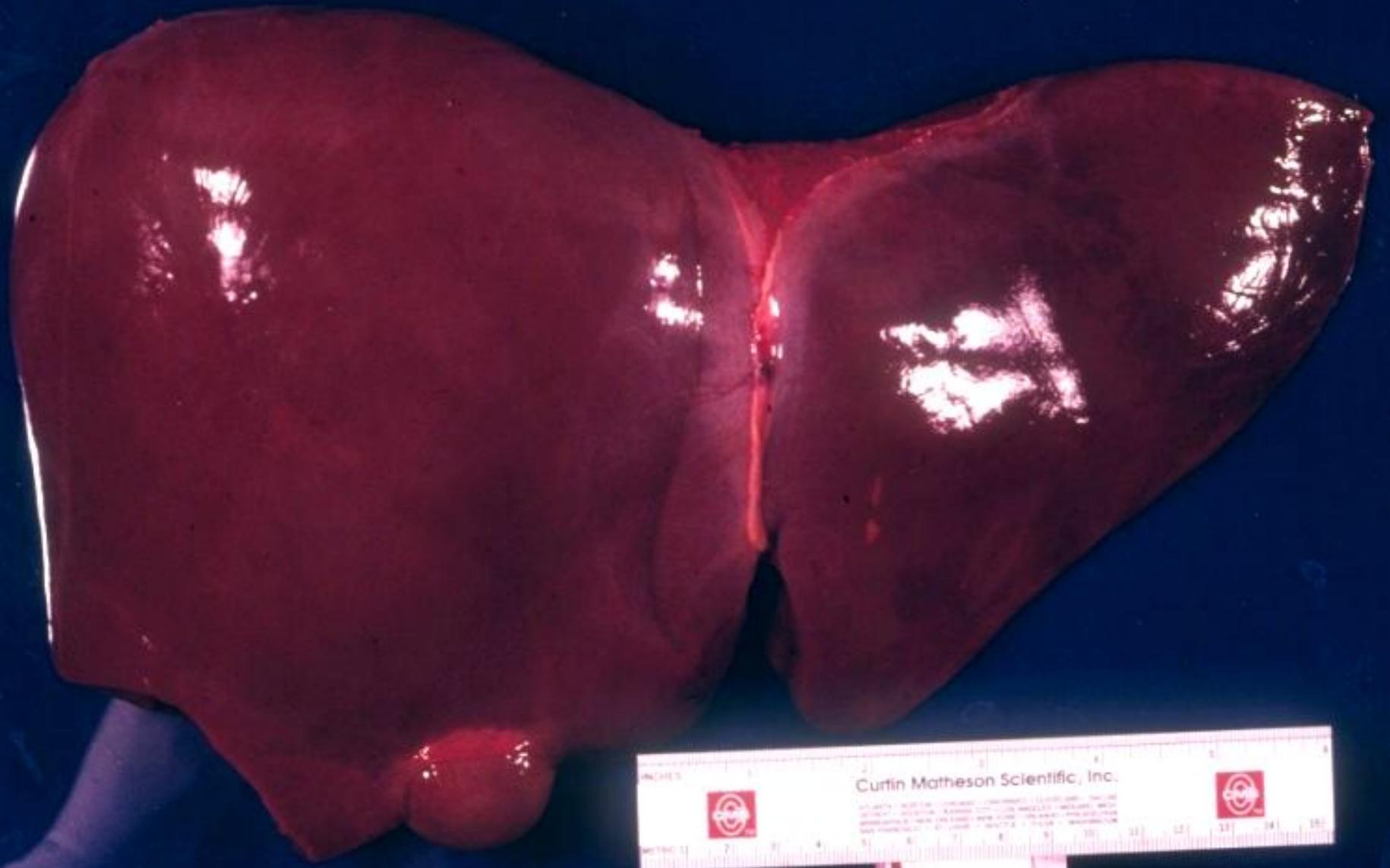
Hospital Clínico Universidad de Chile

Resumen

- Anatomía normal del hígado
 - Macroanatomía
 - Microanatomía
- Características Patológicas de la Enfermedad Hepática
 - Lesiones Elementales
 - Gradación y Estadiaje
- Falla Hepática
- Tumores

Hígado normal

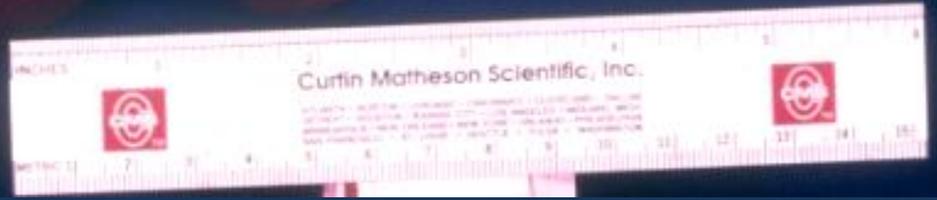
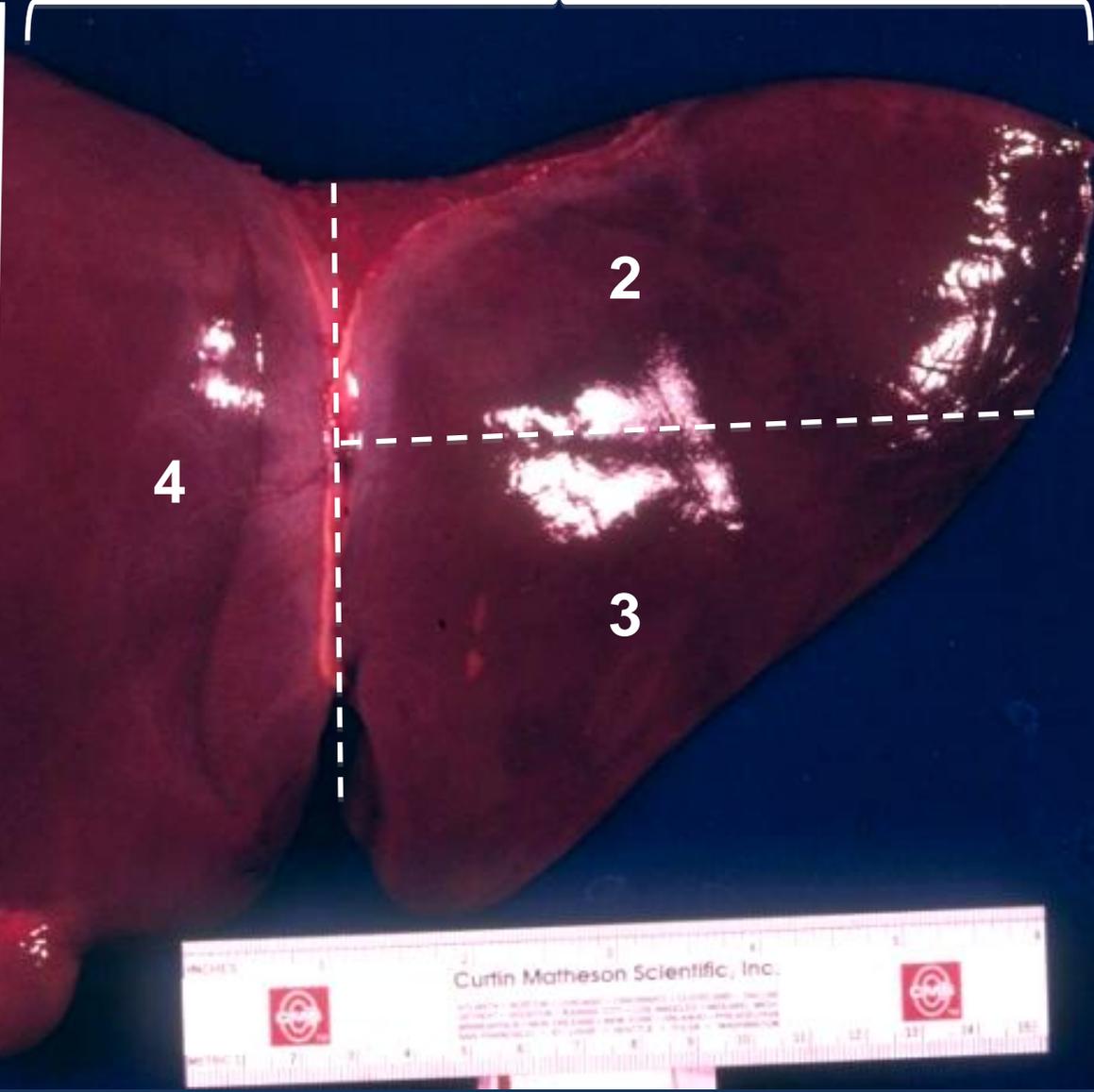
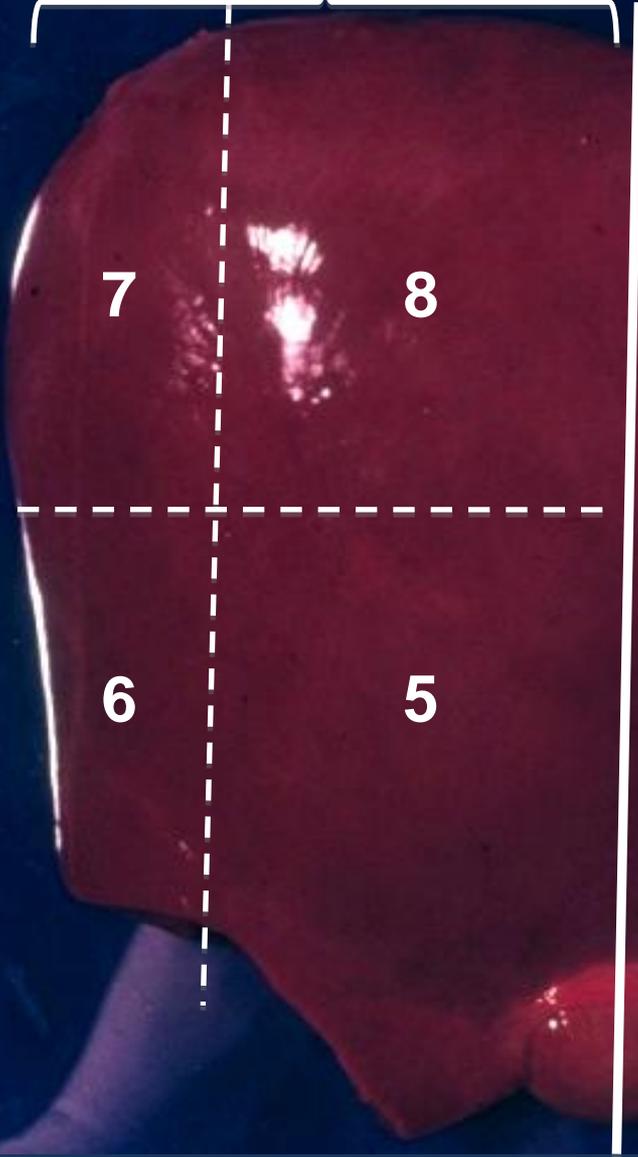
- Se ubica en el cuadrante superior derecho
- Órgano único más grande (1,4-1,6 kg) ~ 2.5% del peso corporal
- Anatomía:
 - Lóbulos derecho e izquierdo



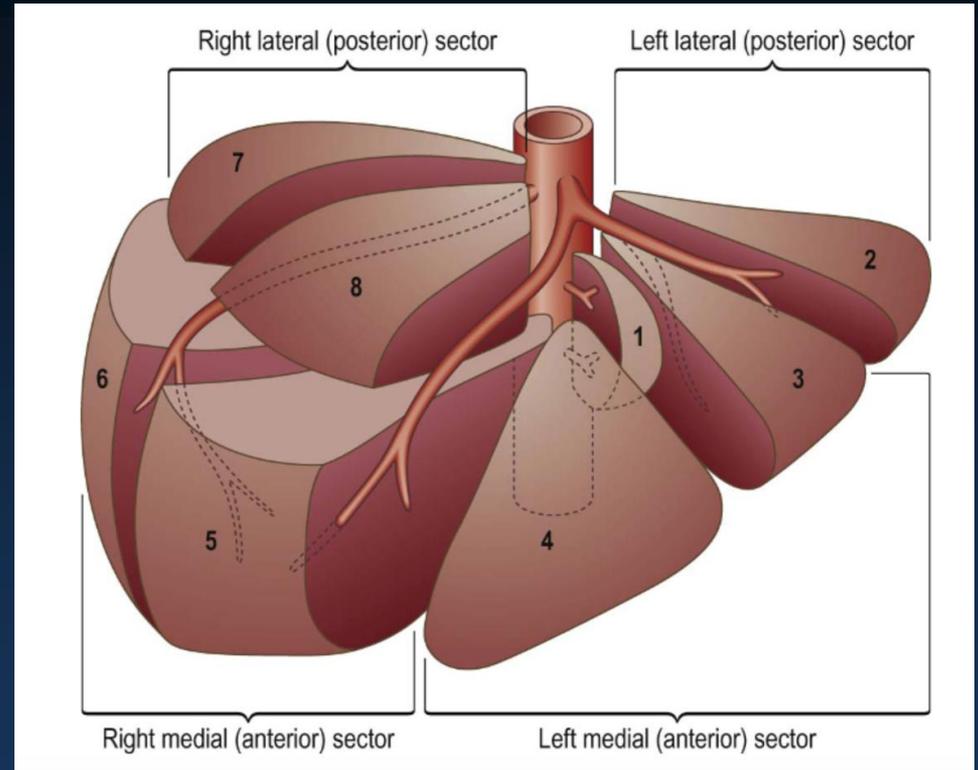
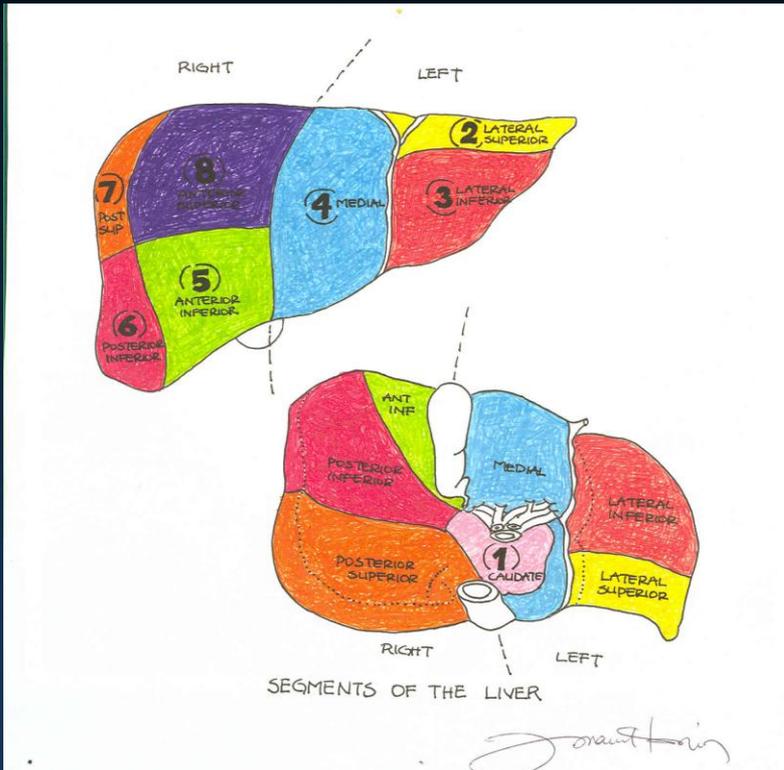
INCHES 0 1 2 3 4
CENTIMETERS 0 1 2 3 4 5 6 7 8 9 10
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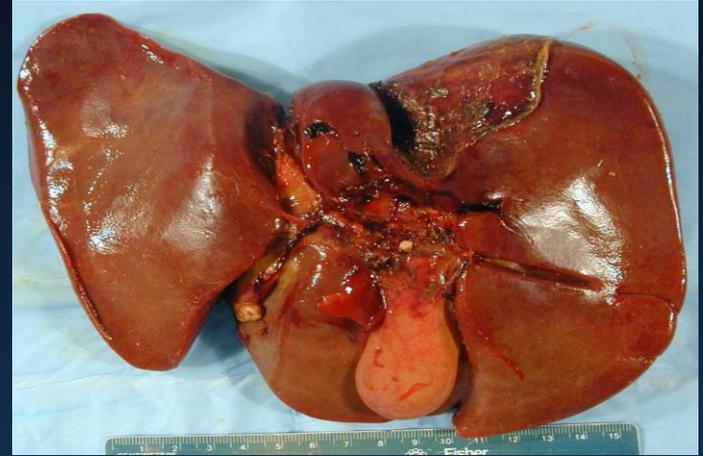


División funcional: segmentos



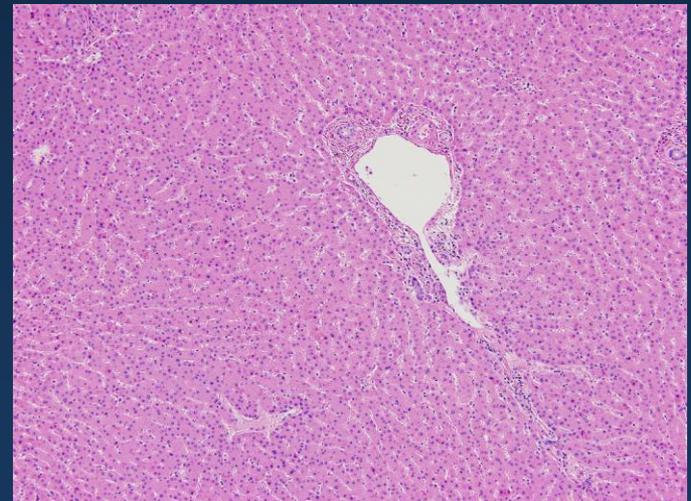
Irrigación sanguínea y drenaje venoso

- Irrigación dual a través del hilio (porta hepatis)
 - Vena porta (60-70%)
 - Arteria hepática (30-40%)
- Drenaje venoso:
 - Venas hepáticas
 - Intersegmentarias
 - VH Derecha, media e izquierda → VCI



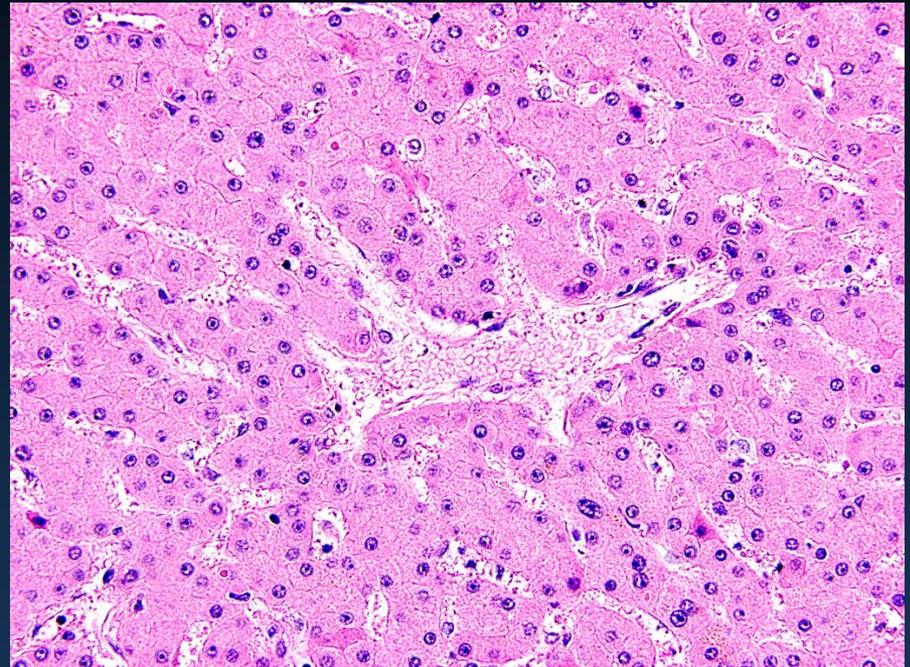
Histología

- Unidades funcionales del hígado:
 - Lobulillo o acino
 - Espacios o tractos portales
 - Vena (venula) central → vena hepática
 - Hepatocitos y canalículo biliar
 - Sinusoides, células sinusoidales y perisinusoidales.

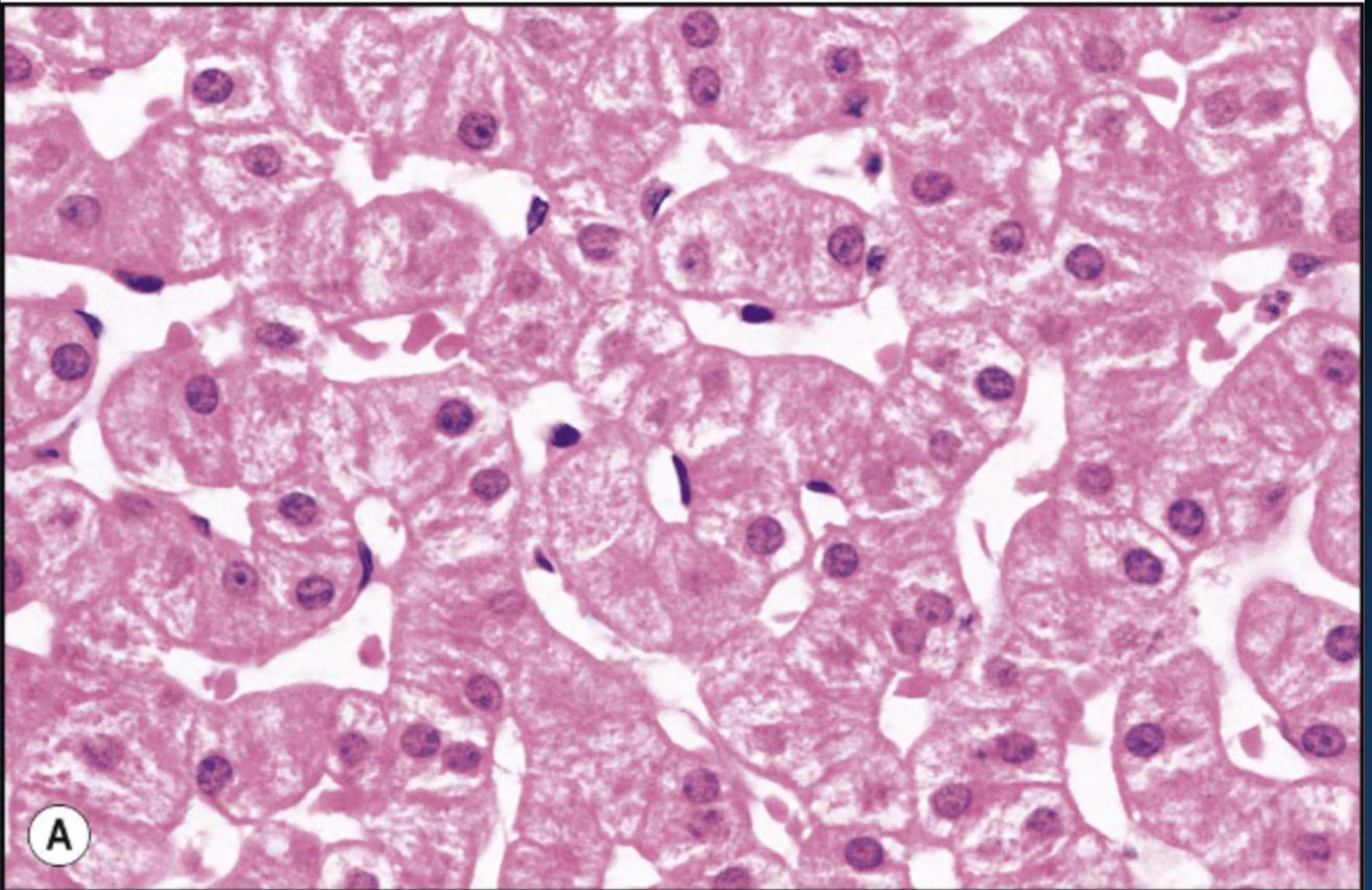


Microarquitectura: lobulillo/acino

- Trabéculas
 - Cordones de hepatocitos
- Placa limitante
 - Primera línea de hepatocitos en contacto con el espacio porta.
- Sinusoides
 - Células endoteliales fenestradas
- Células de Kupffer
 - Sistema fagocítico-mononuclear
- Células hepáticas estrelladas

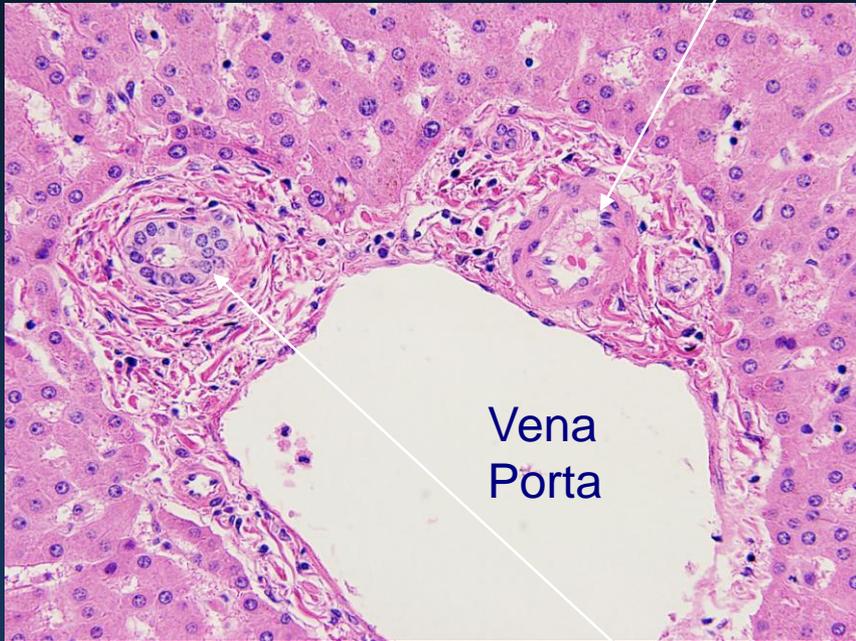


Hepatocitos y canalículo biliar



Espacio Porta

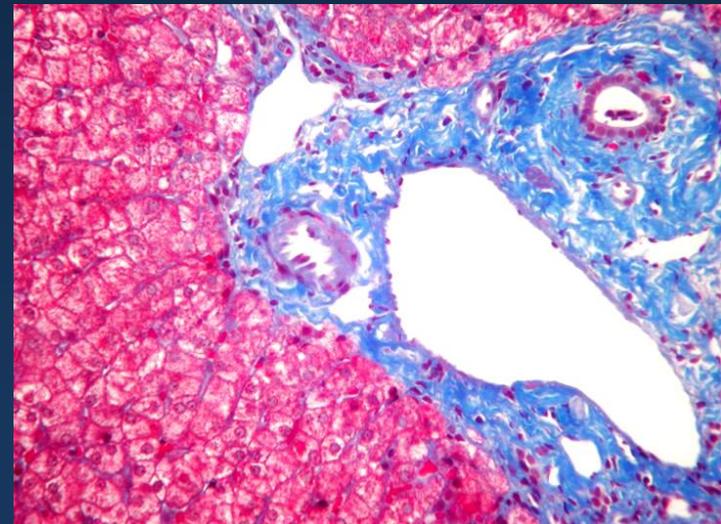
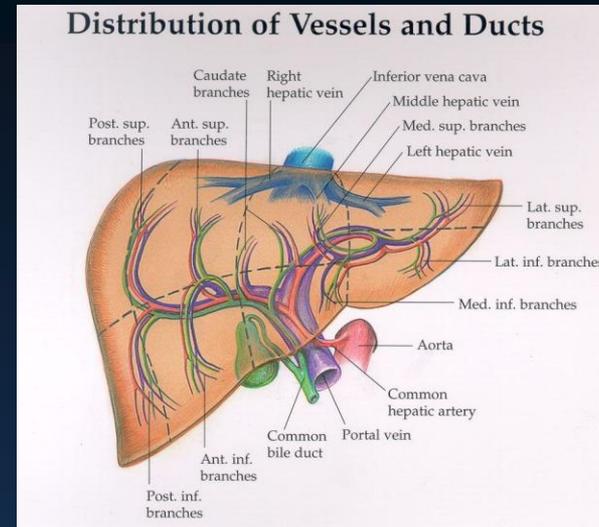
Arteria
Hepática



Ducto
Biliar

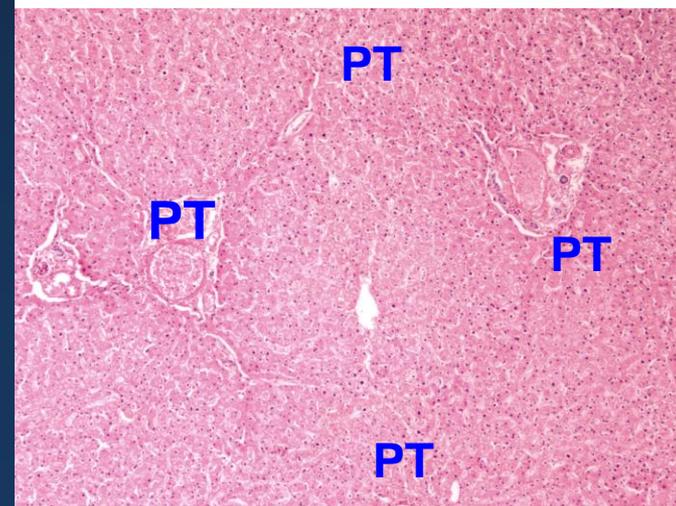
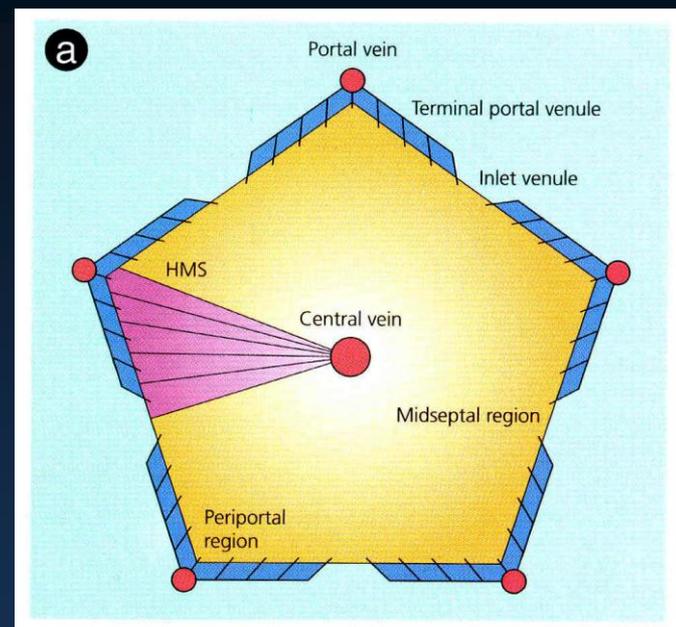
Ductos biliares

- Irrigados por arterias hepáticas via plexo de capilares peribiliares
- Drenan bilis formada en los hepatocitos secretada a canaliculos, canales de Hering y ductos biliares intra y extrahepáticos.



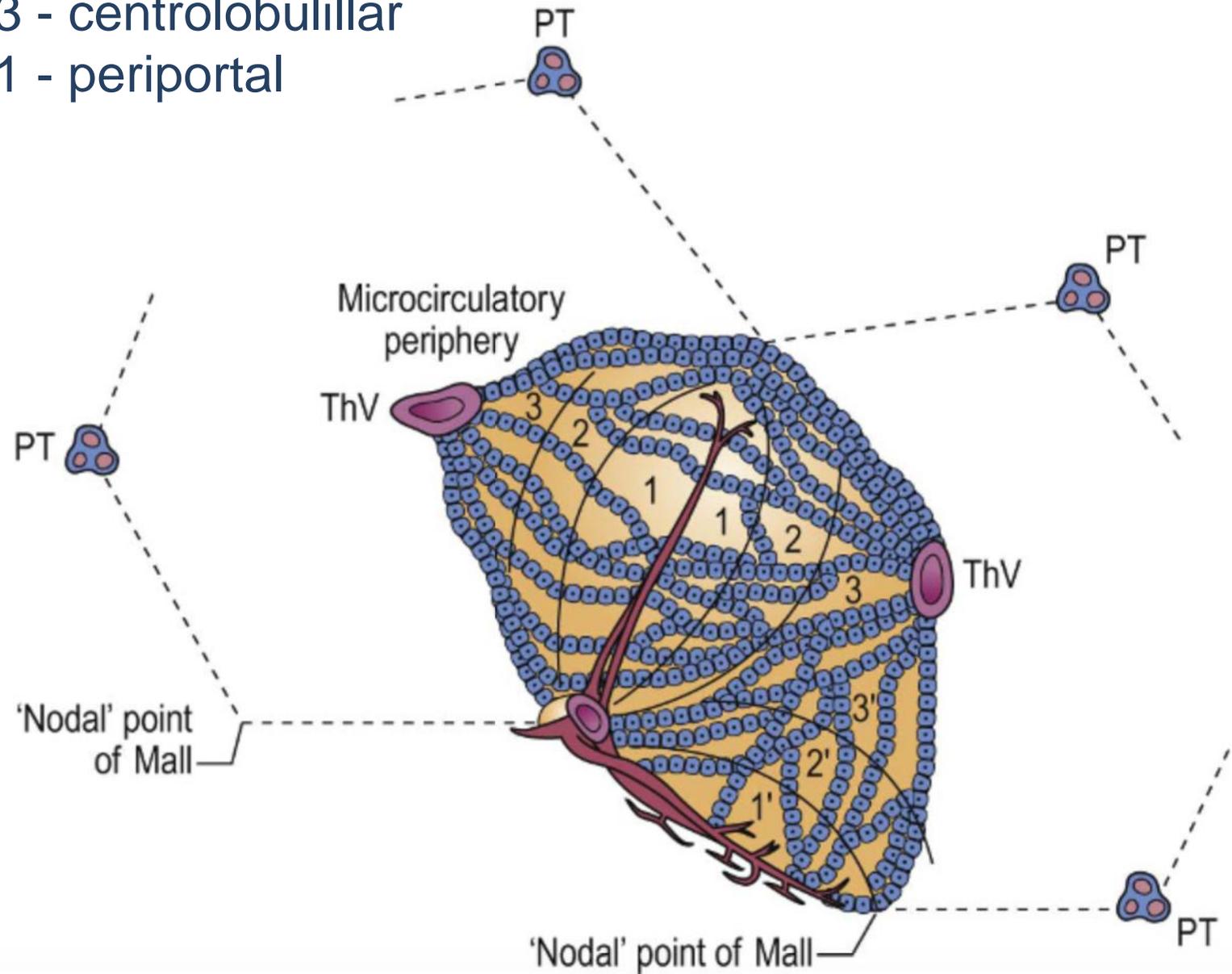
Unidad funcional

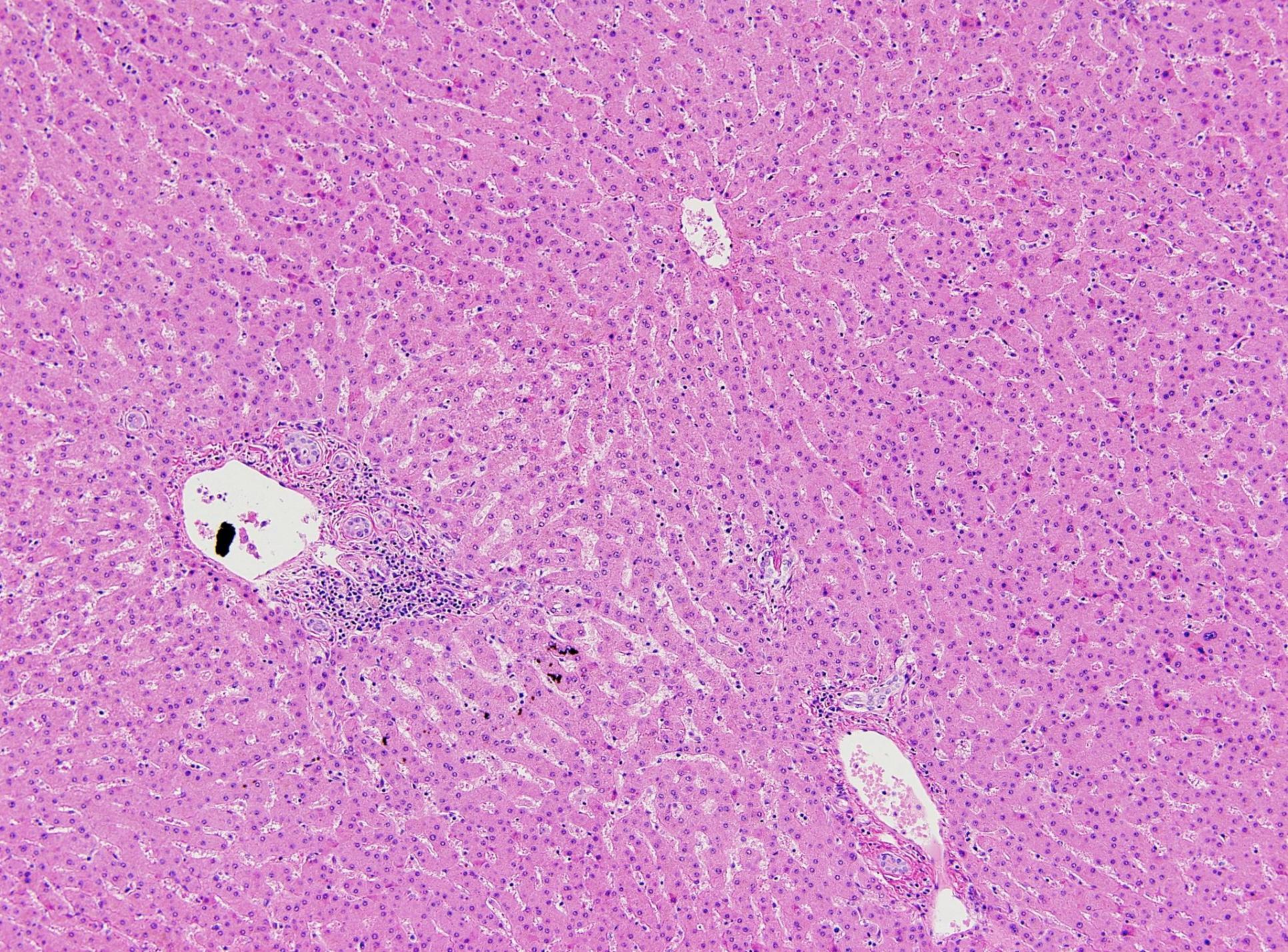
- Lobulillo clásico
 - Orientado alrededor de venas hepáticas terminales (vena central)
 - hepatocitos centrolobulillares
 - Espacios porta en la periferia
 - hepatocitos periportales

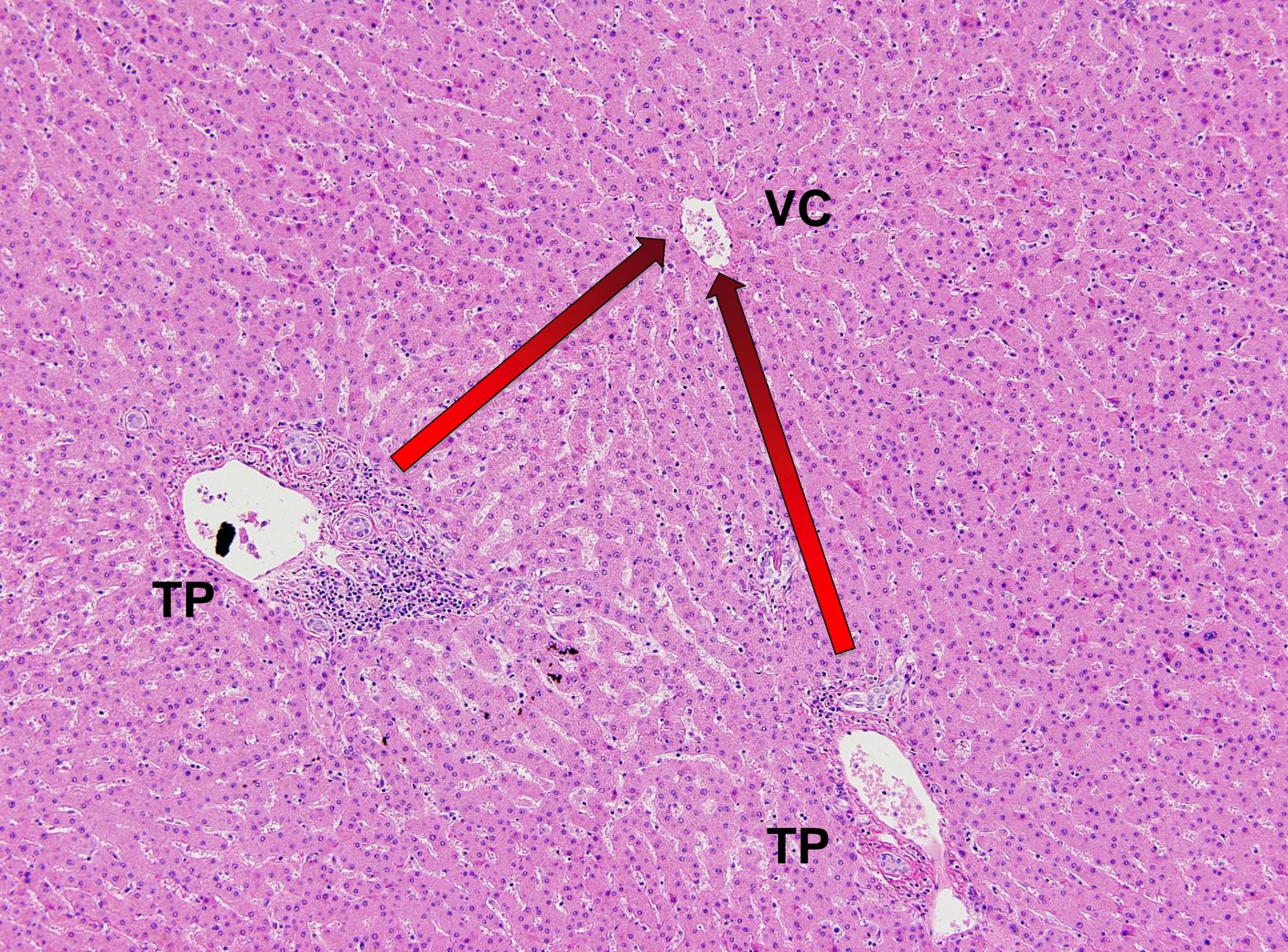


• Acino

- 3 zonas
- Zona 3 - centrolobulillar
- Zona 1 - periportal



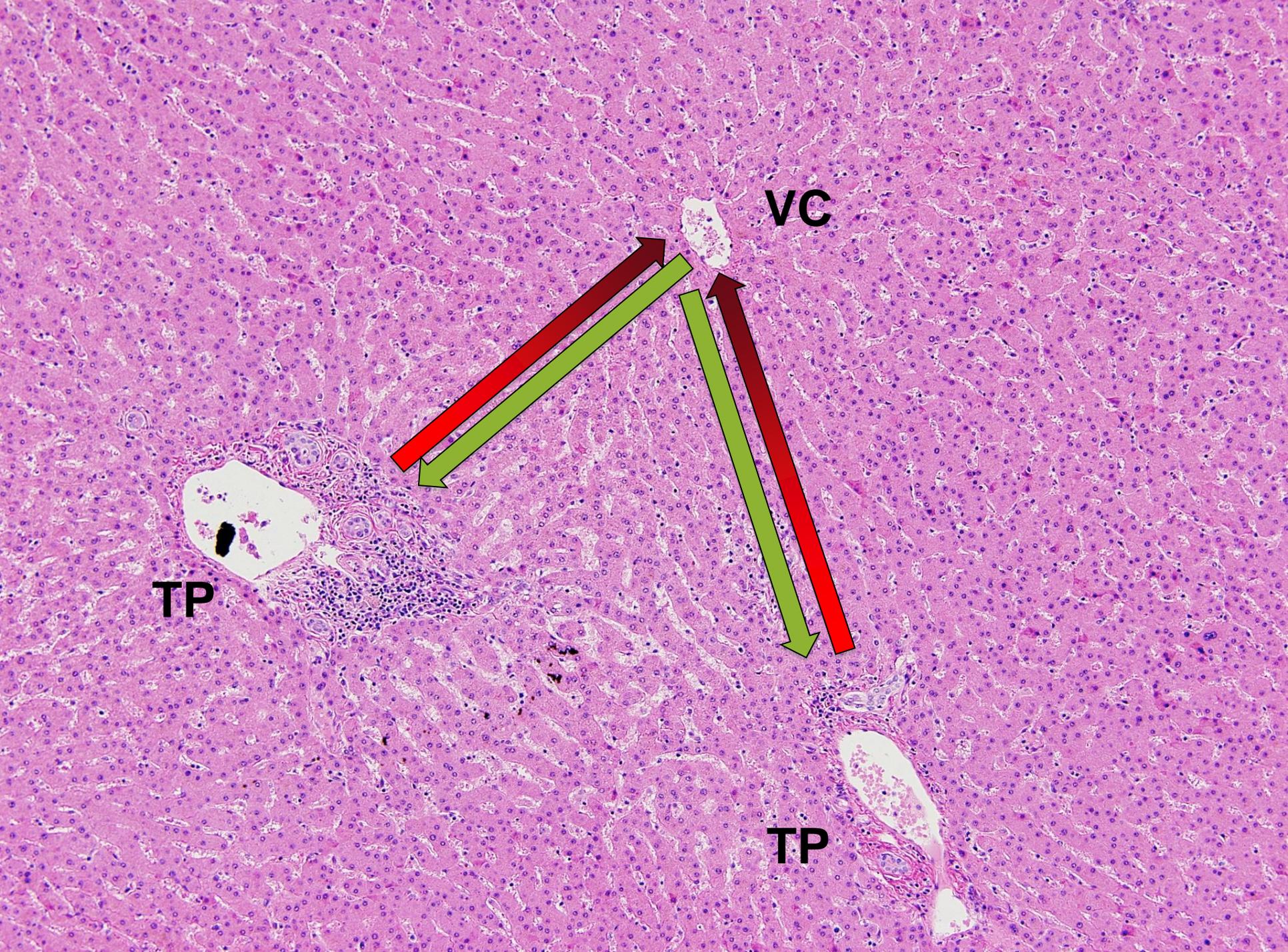




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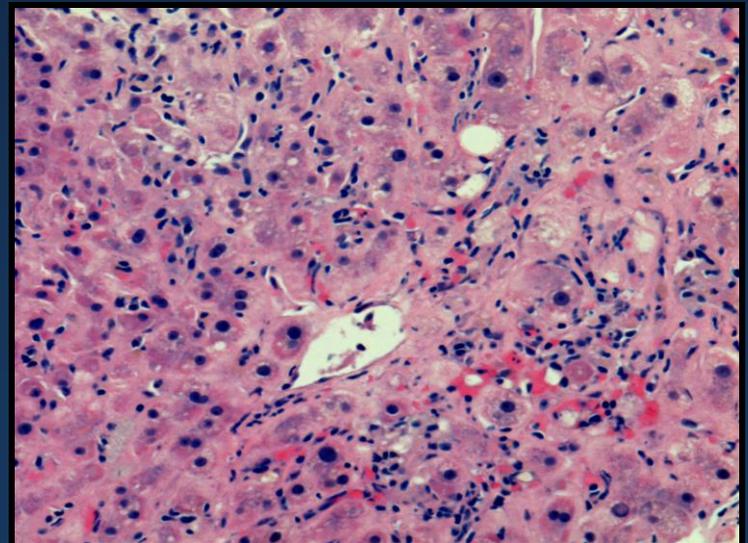
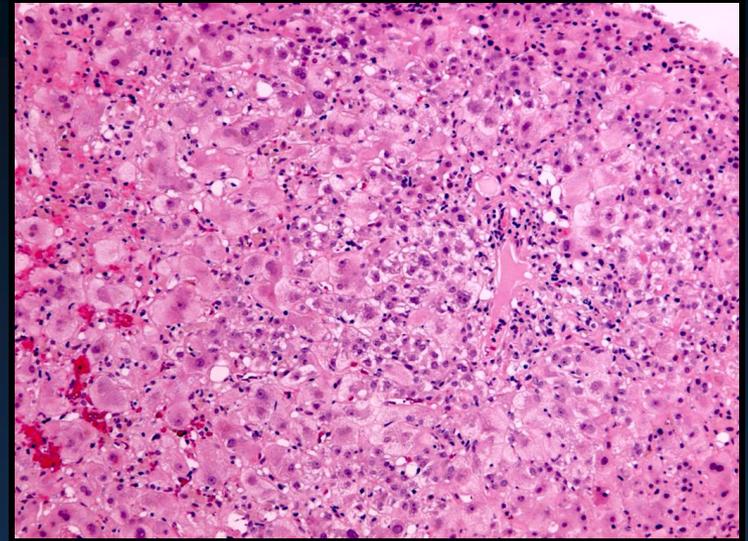
Características Patológicas de la Enfermedad Hepática

HEPATITIS

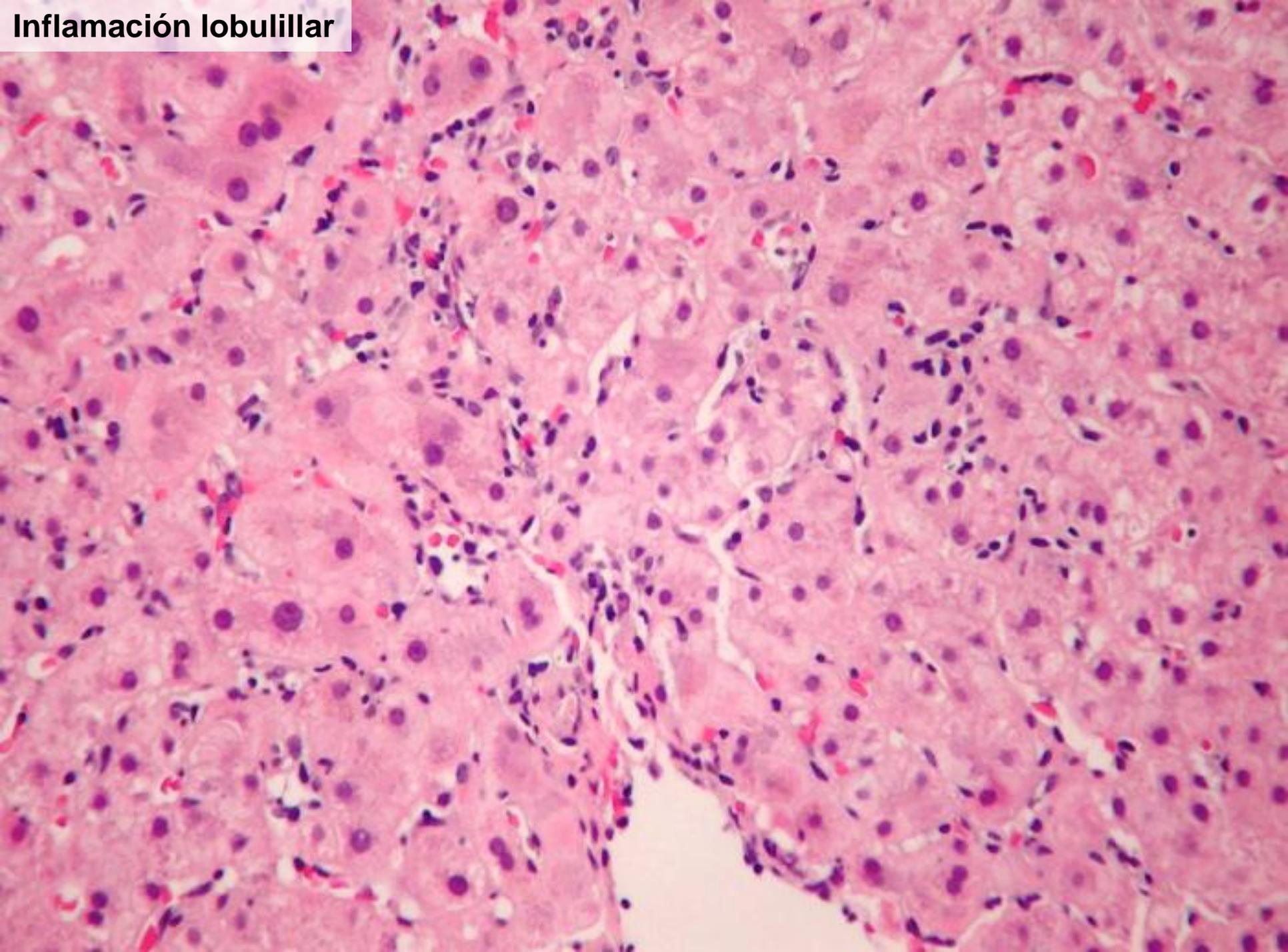
Hepatitis

- Daño hepático (inflamación)
 - Agudo < 6 meses
 - Crónico > 6 meses
- Hepatocitos apoptóticos
- Inflamación lobulillar
- Inflamación portal

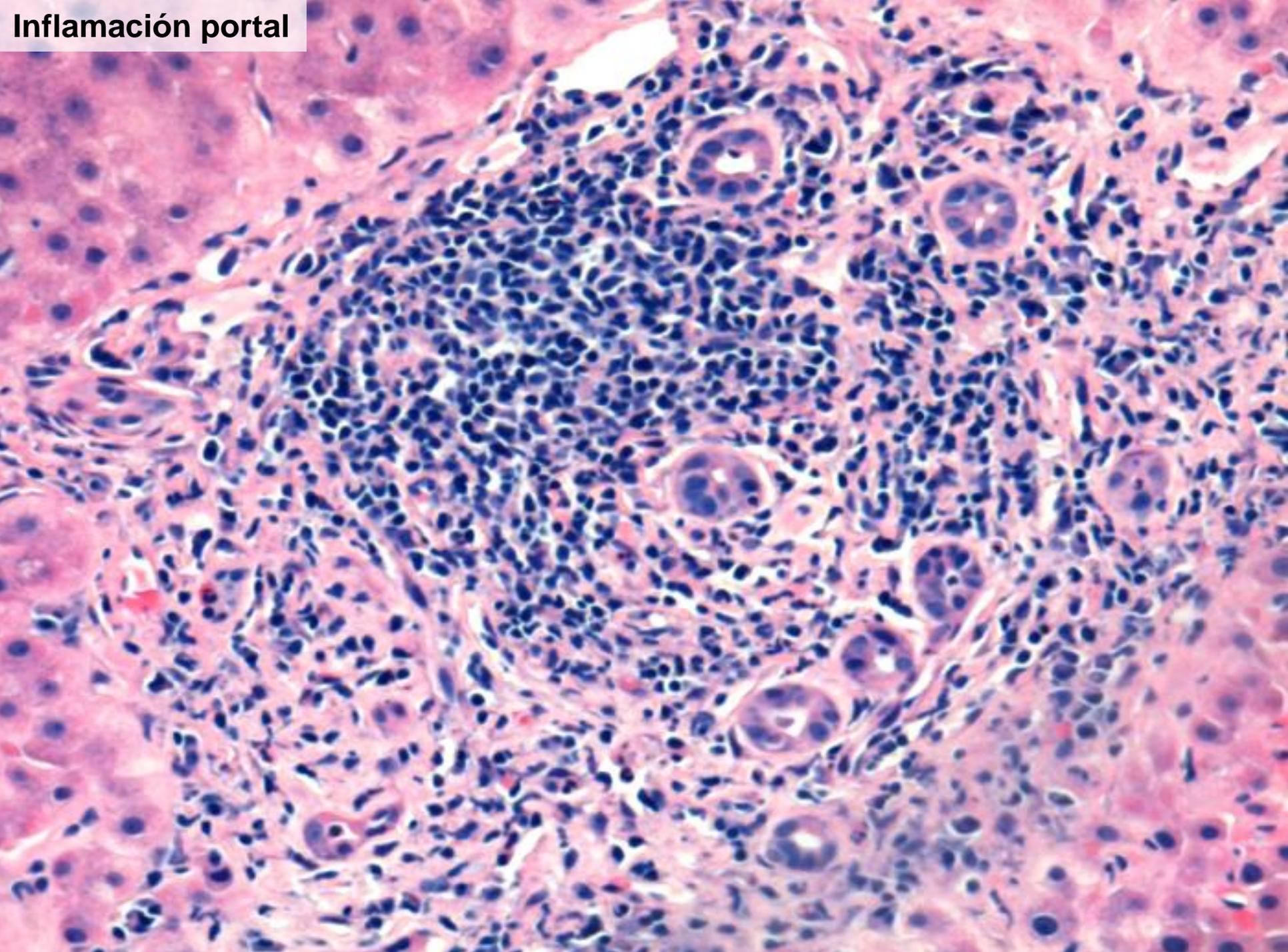
- *Hallmark = muerte de células hepáticas



Inflamación lobulillar



Inflamación portal



Hepatitis: causas

Infectious

Viral hepatitis – hepatotropic

Viral hepatitis – opportunistic

Bacterial

Fungal

Parasitic

Helminthic

Immune-mediated

Autoimmune hepatitis

Primary biliary cirrhosis

Primary sclerosing cholangitis

Transplant rejection

Graft-versus-host disease

Drug- and toxin-induced hepatotoxicity

Alcoholic liver disease

Therapeutic agents (including complementary medicines and drugs of abuse)

Metabolic

Inherited metabolic disease

Acquired metabolic derangement

Non-alcoholic fatty liver disease

Mechanical

Obstructive cholestasis

Vascular disorders

Environmental

Environmental toxins

Heat stroke

Hepatitis: causas

Infectious

Viral hepatitis – hepatotropic

Viral hepatitis – opportunistic

Bacterial

Fungal

Parasitic

Helminthic

Immune-mediated

Autoimmune hepatitis

Primary biliary cirrhosis

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Características Patológicas de la Enfermedad Hepática

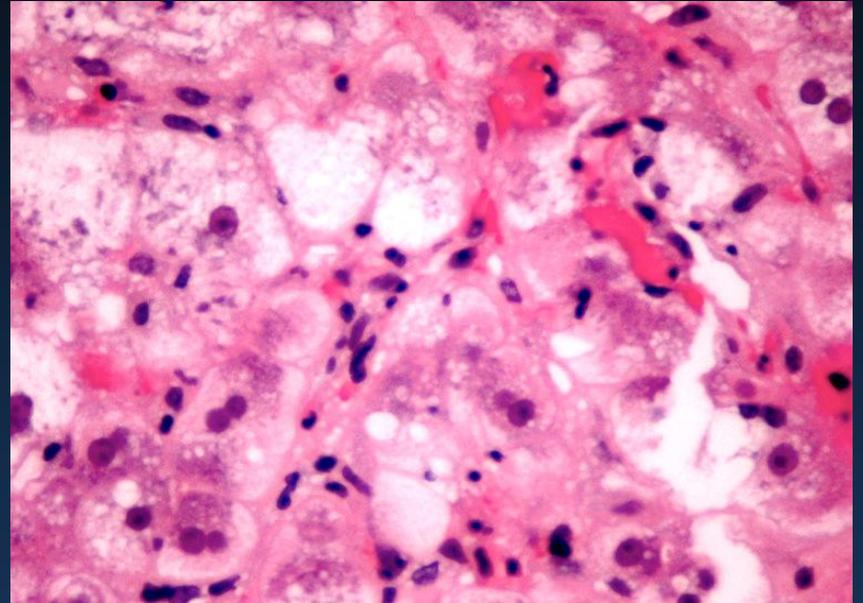
LESIONES ELEMENTALES

Lesiones Elementales

- Degeneración
 - Balonamiento
 - “Plumosa”
- Muerte celular
 - Apoptosis
 - Necrosis
 - Coagulativa/Isquémica
 - Distribución
- Hepatitis de Interfase
- Esteatosis
- Cuerpos de Mallory-Denk
- Colangitis
 - Tipos
- Colestasia
- Fibrosis

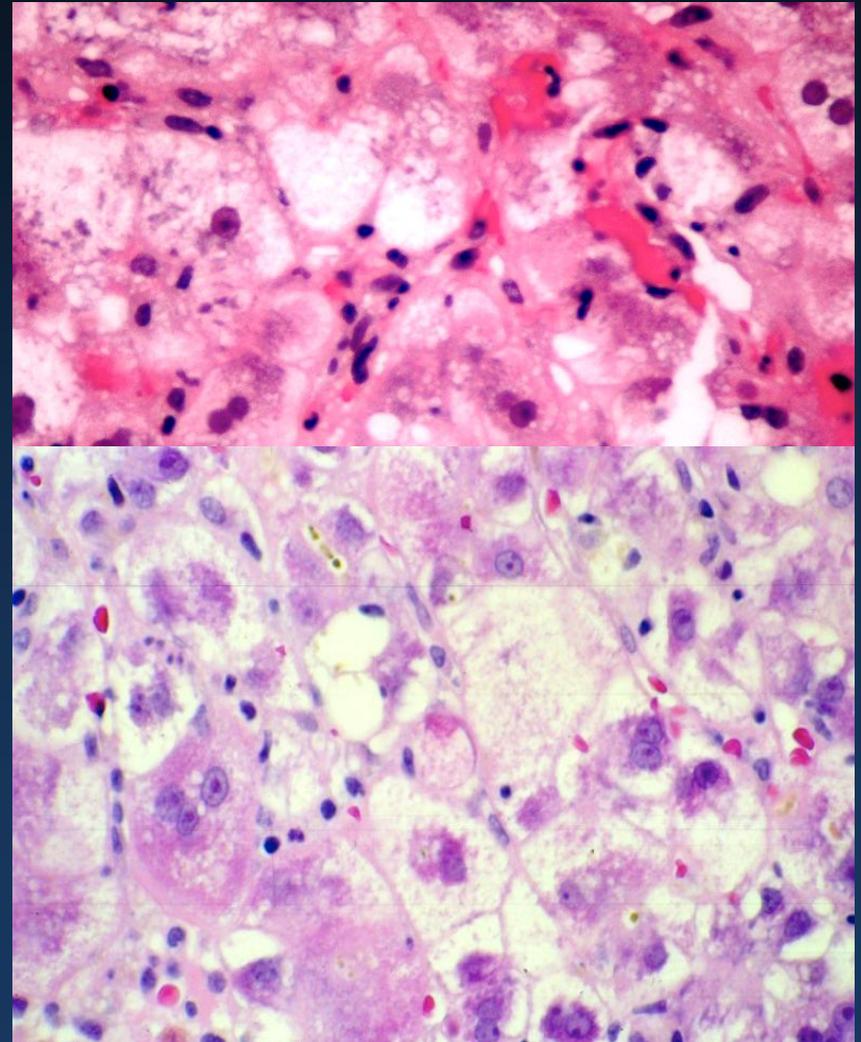
Degeneración

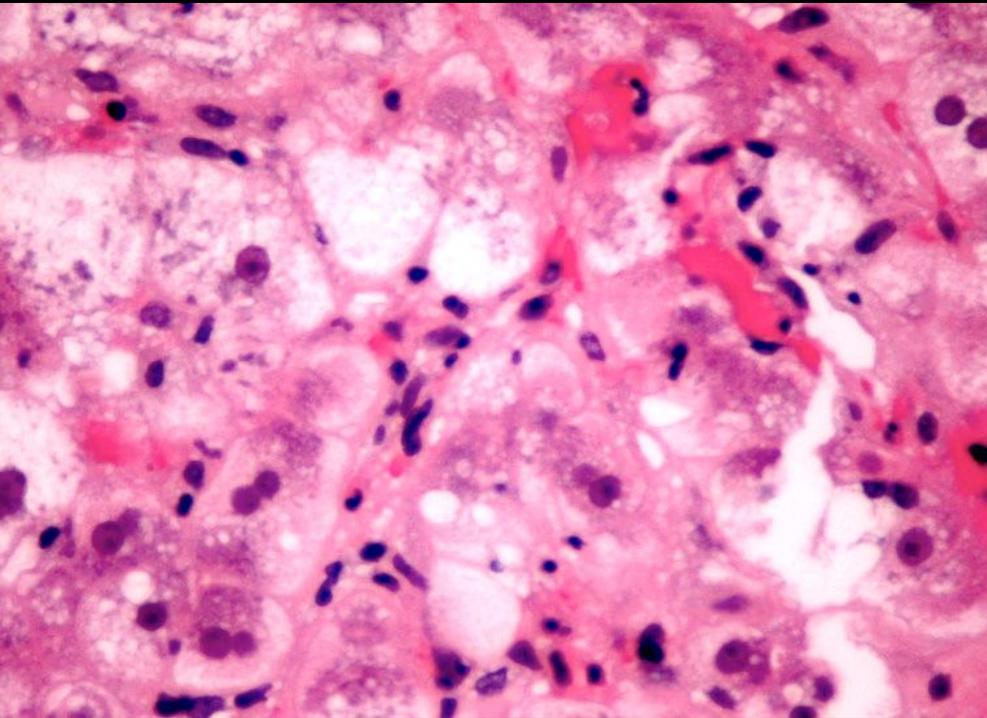
- Balonamiento
 - Organelos citoplasmáticos agrupados y grandes espacios claros



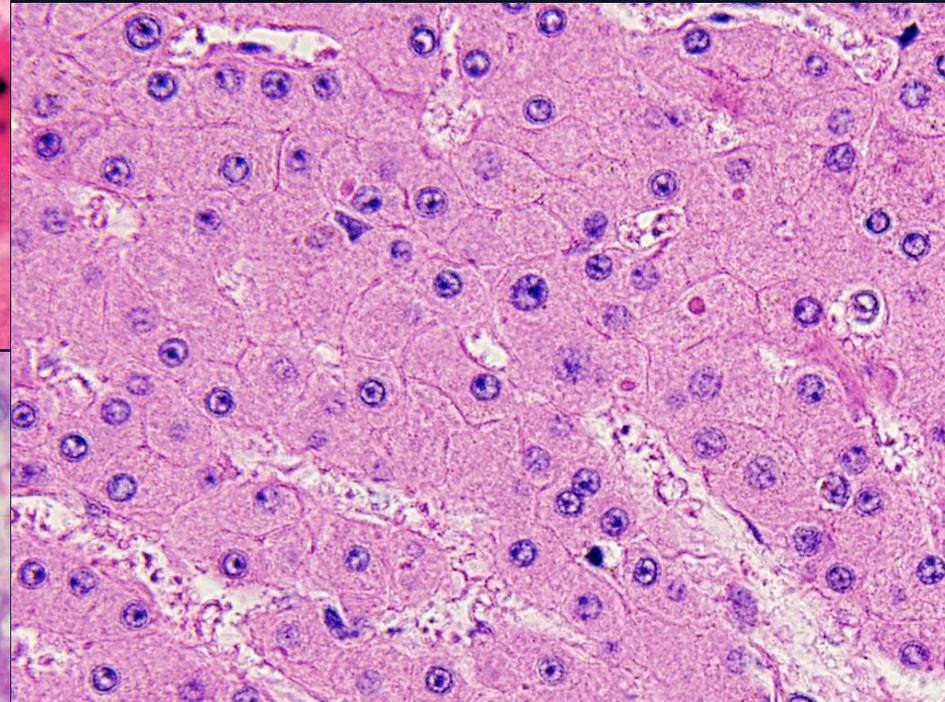
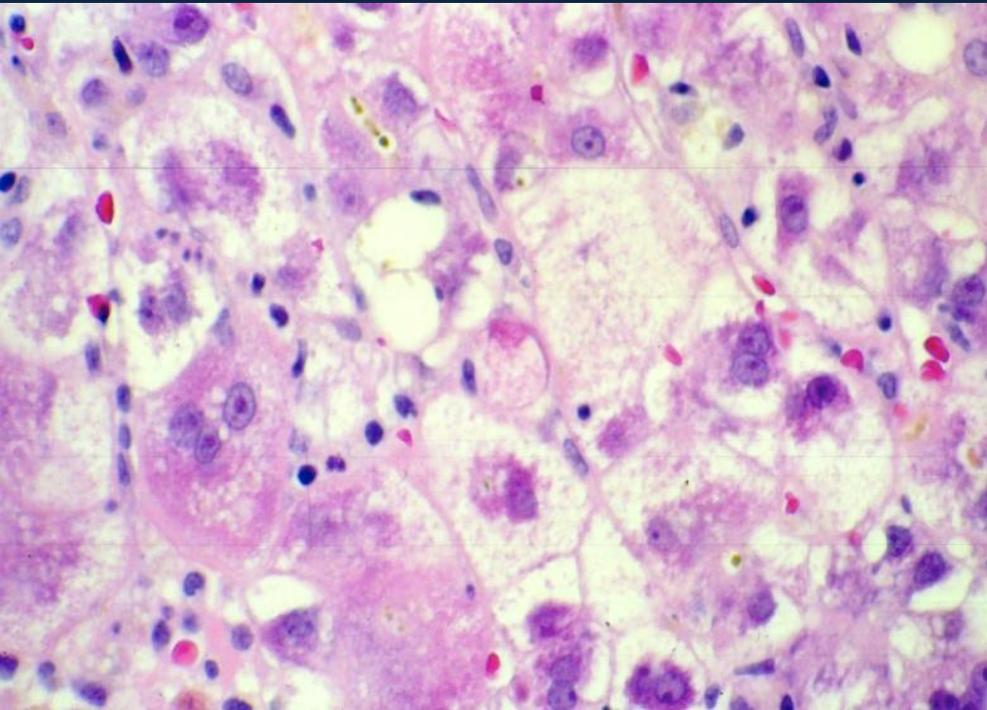
Degeneración

- Balonamiento
 - Organelos citoplasmáticos agrupados y grandes espacios claros
- “Plumosa” (estasis de colatos)
 - Daño colestásico → citoplasma espumoso





Balonamiento

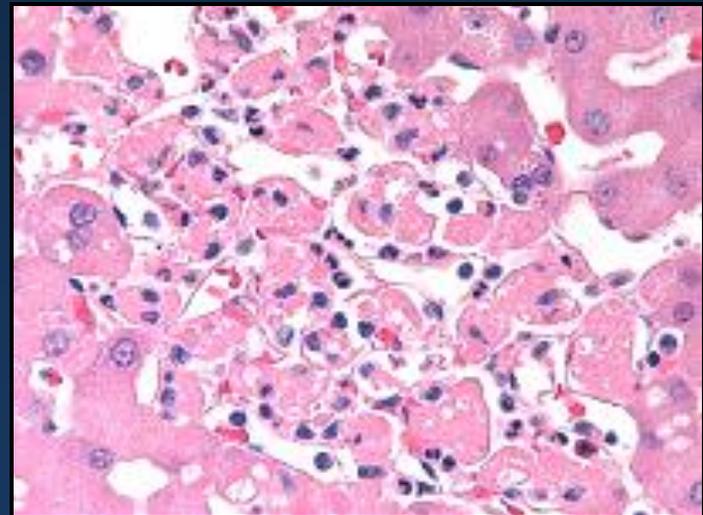
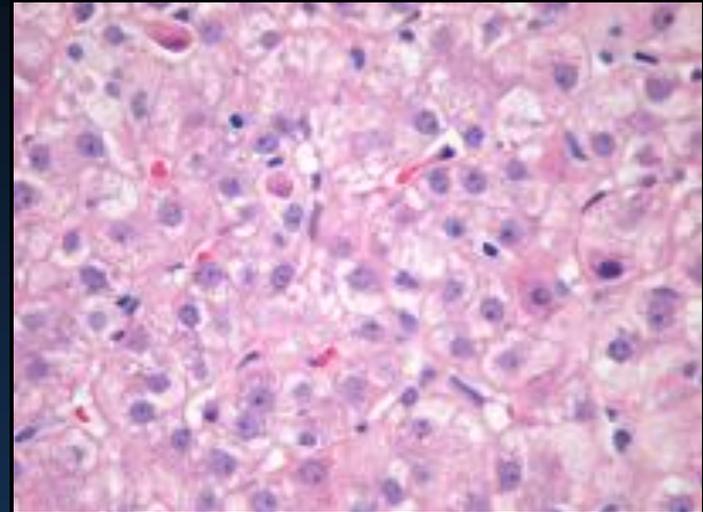


Hepatocitos normales

Deg. plumosa

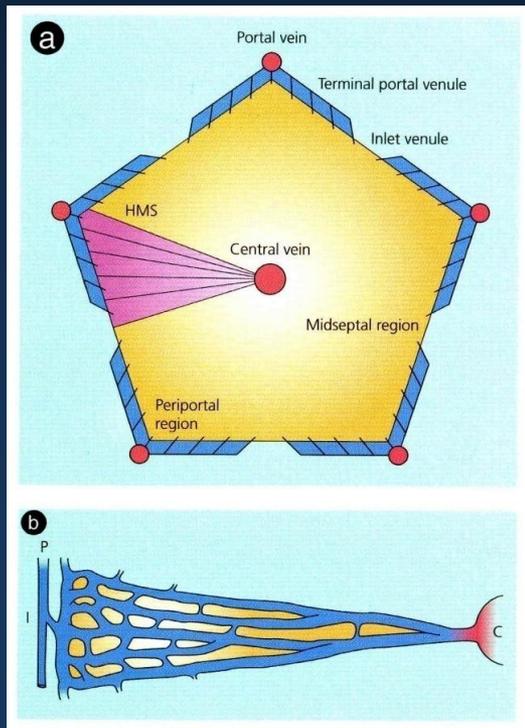
Muerte celular

- Apoptosis (muerte celular)
 - Hepatocitos aislados de menor tamaño, picnóticos y eosinofílicos.
- Necrosis coagulativa/ isquémica
 - Células momificadas



Necrosis: distribución

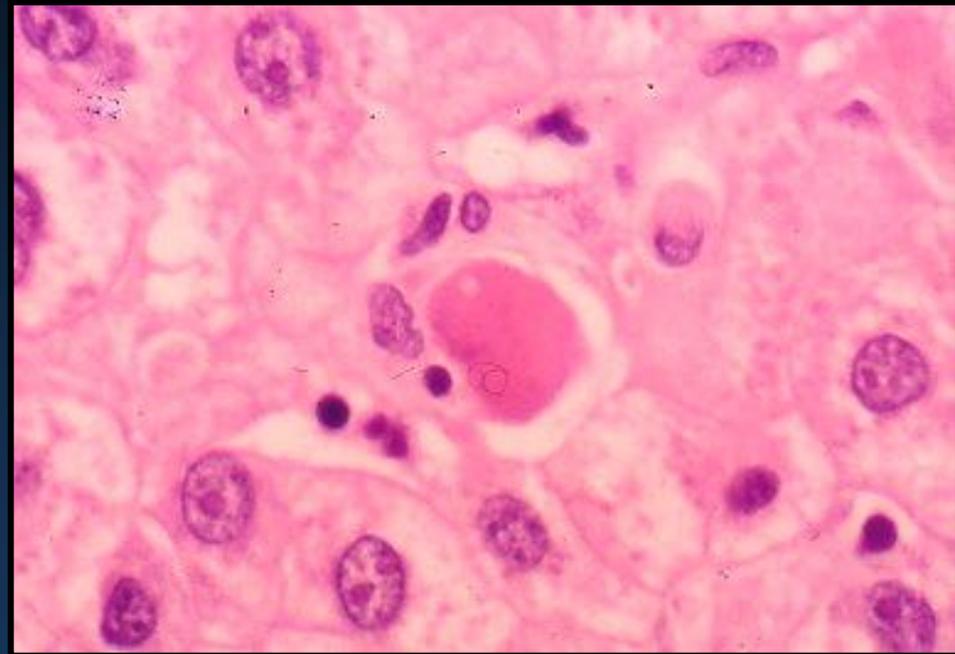
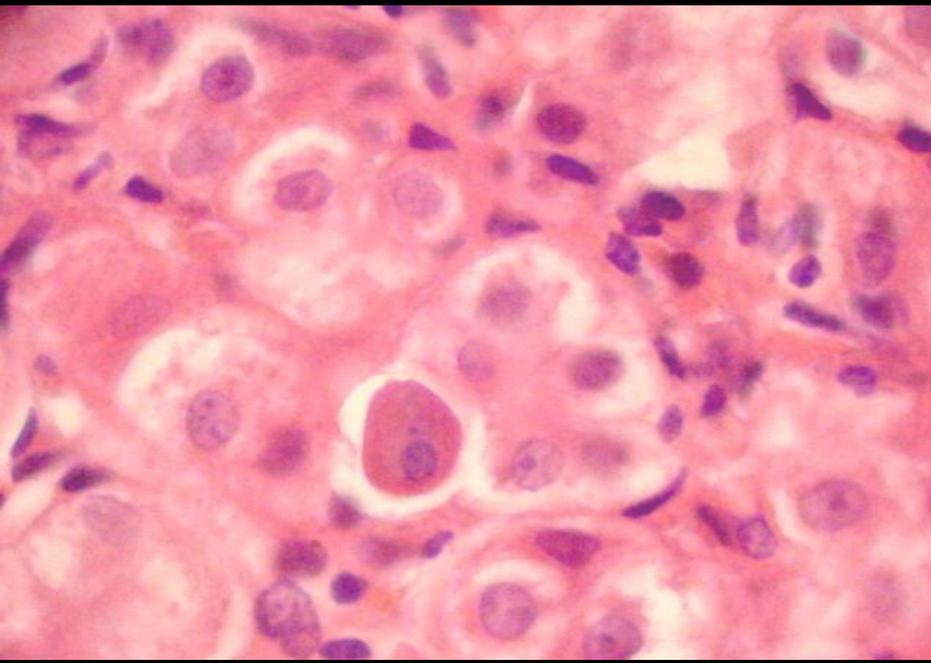
- Zona media (zona 2)
- Periportal (zona 1)
- Centrolobulillar (zone 3)



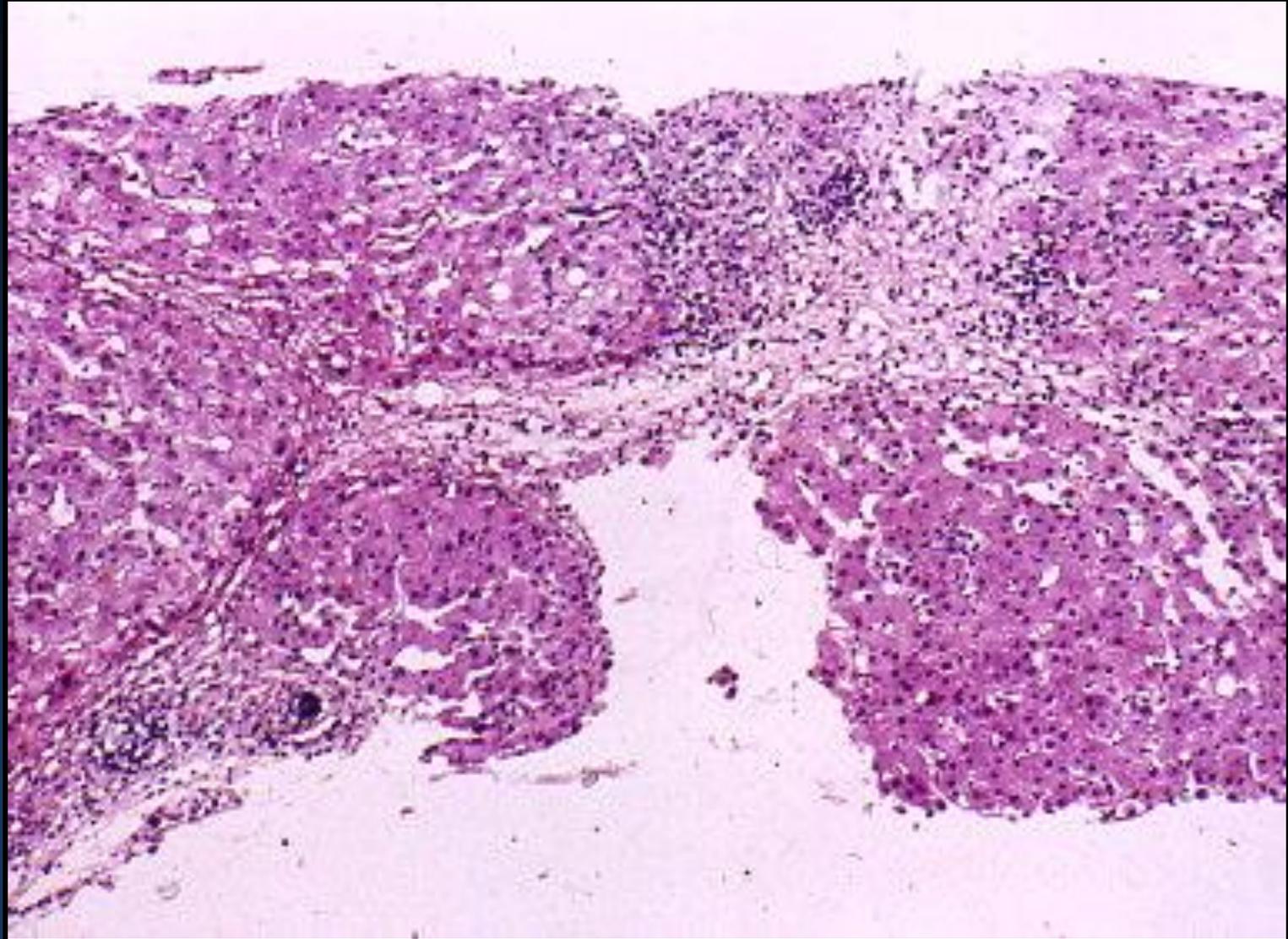
Otros términos:

- Focal o “spotty”
- Necrosis en puente
- Necrosis hepática submasiva
- Necrosis hepática masiva
- Falla hepática

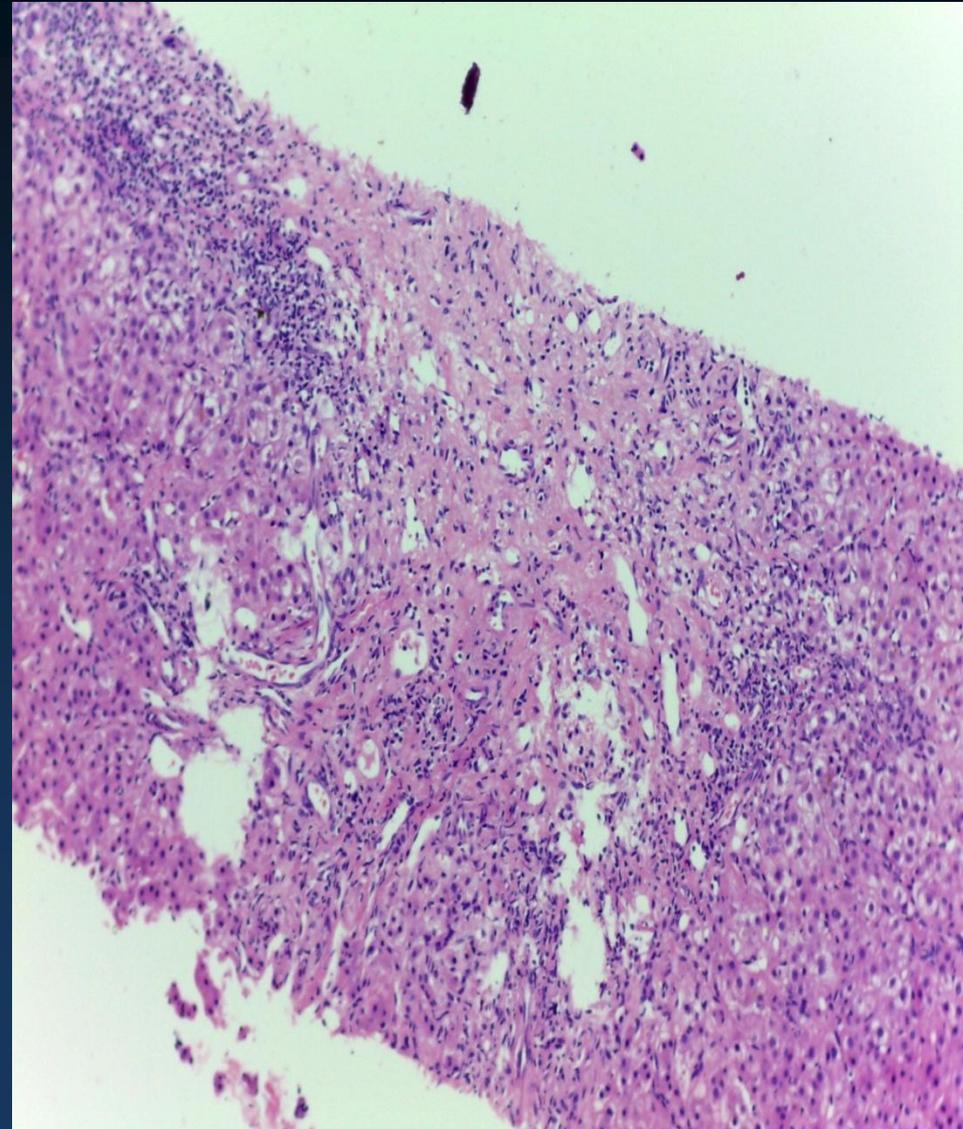
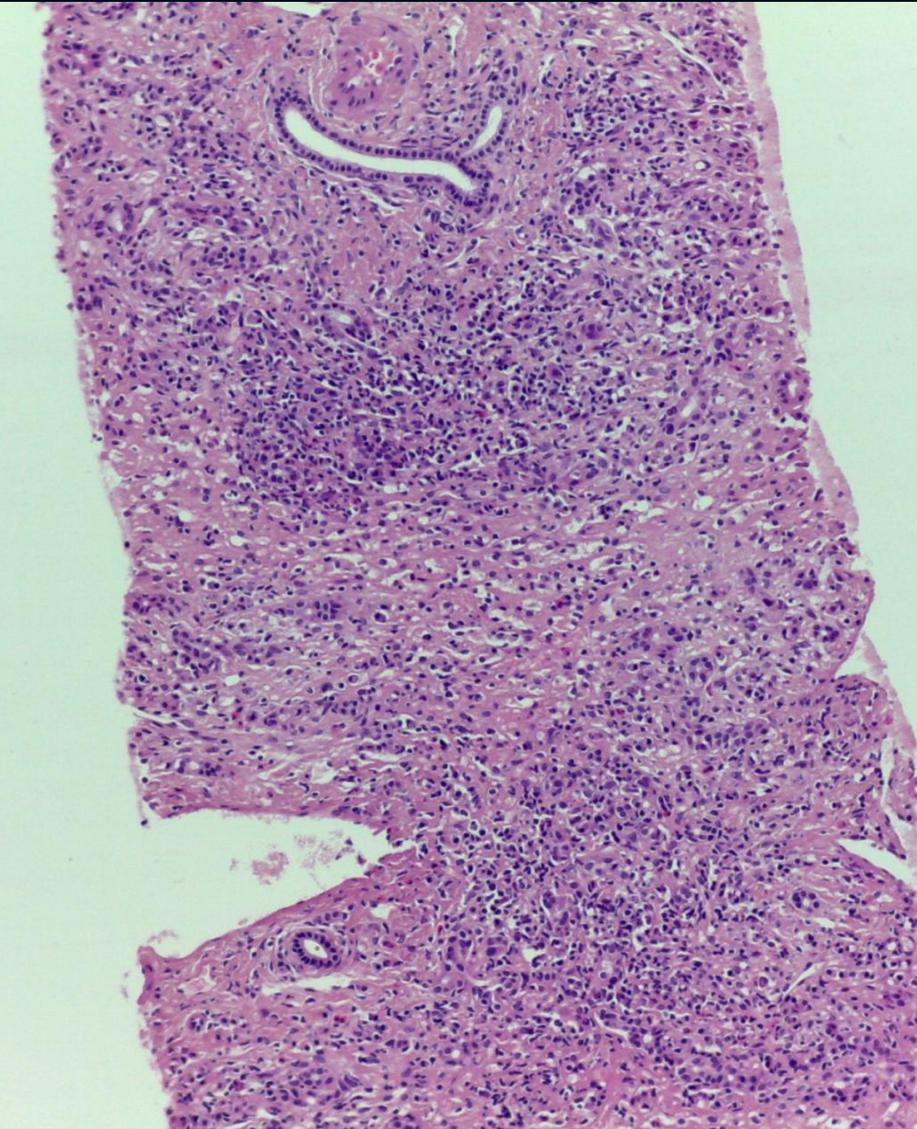
Apoptosis – Focal – “Spotty”



Necrosis confluente

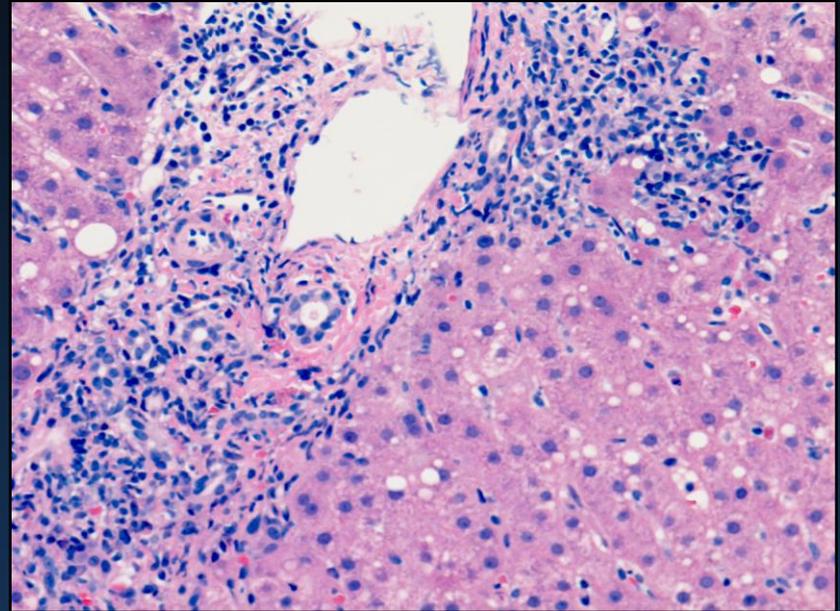


Necrosis confluente



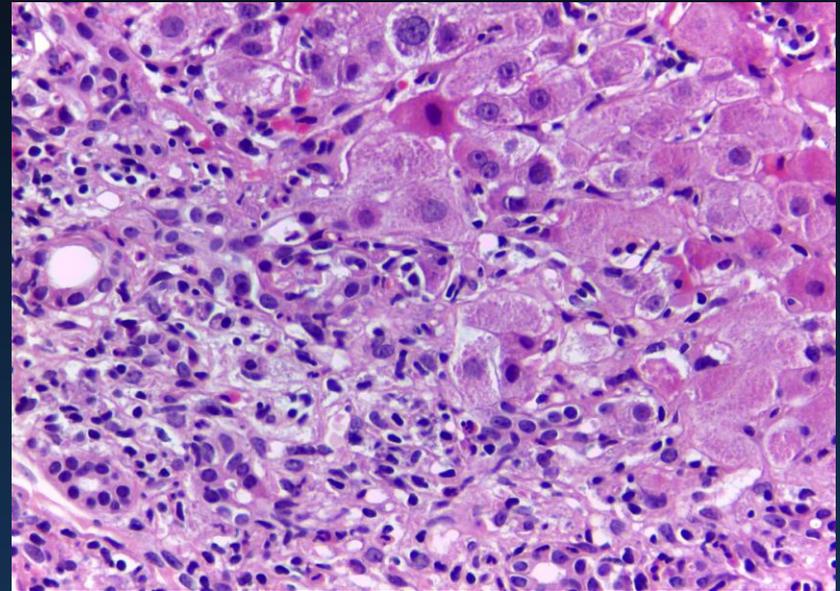
Hepatitis de Interfase

- Conocida antes como “necrosis en sacabocado”
- Células inflamatorias se extienden más allá del límite del espacio porta (placa limitante)

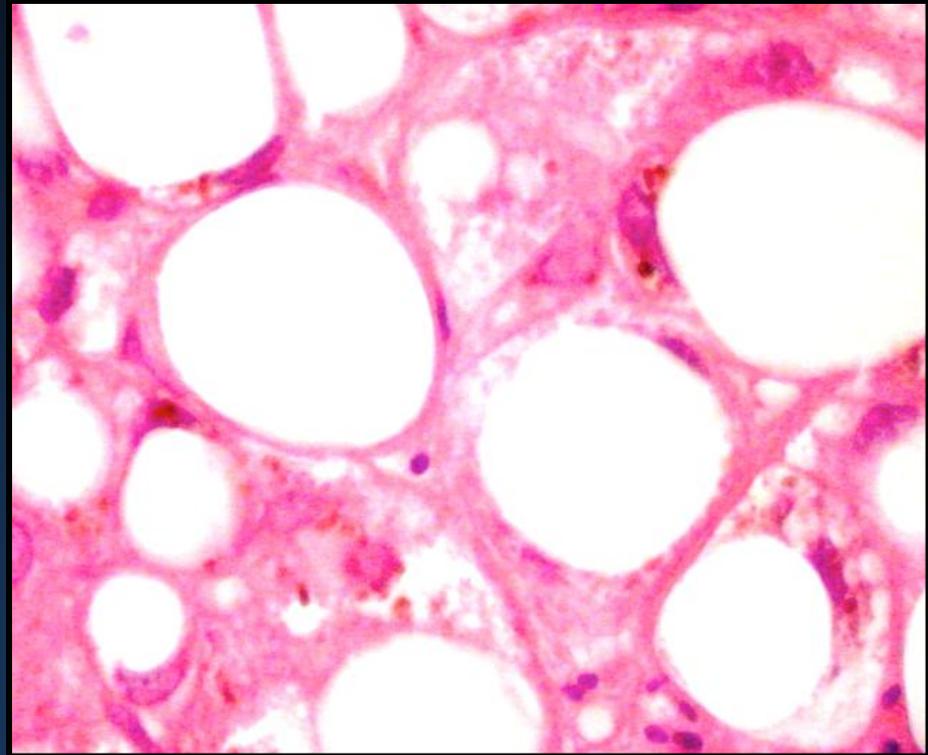
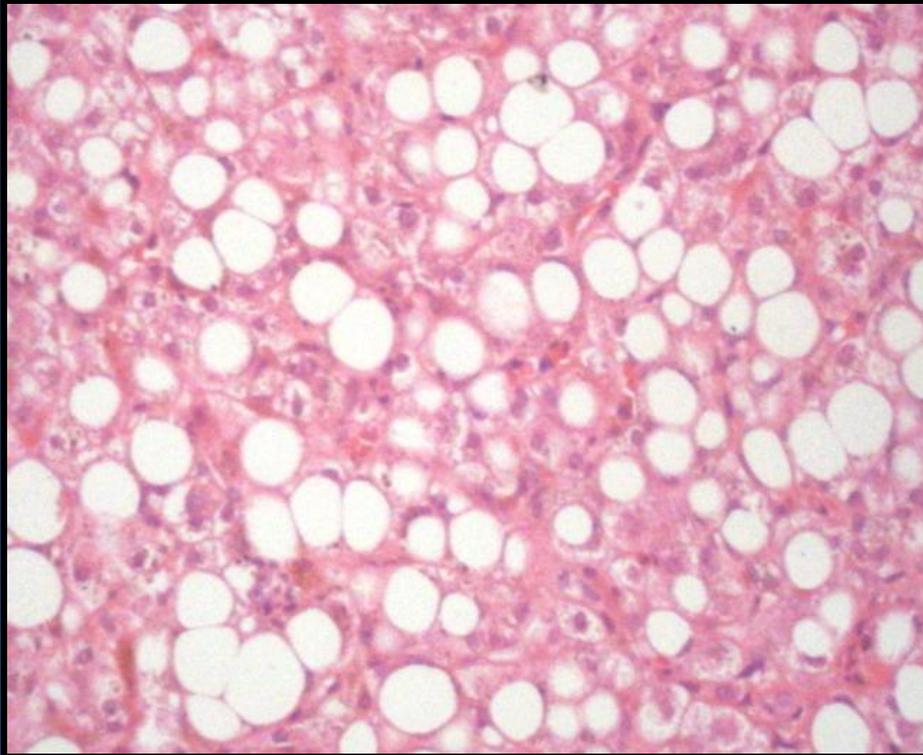


Hepatitis de Interfase

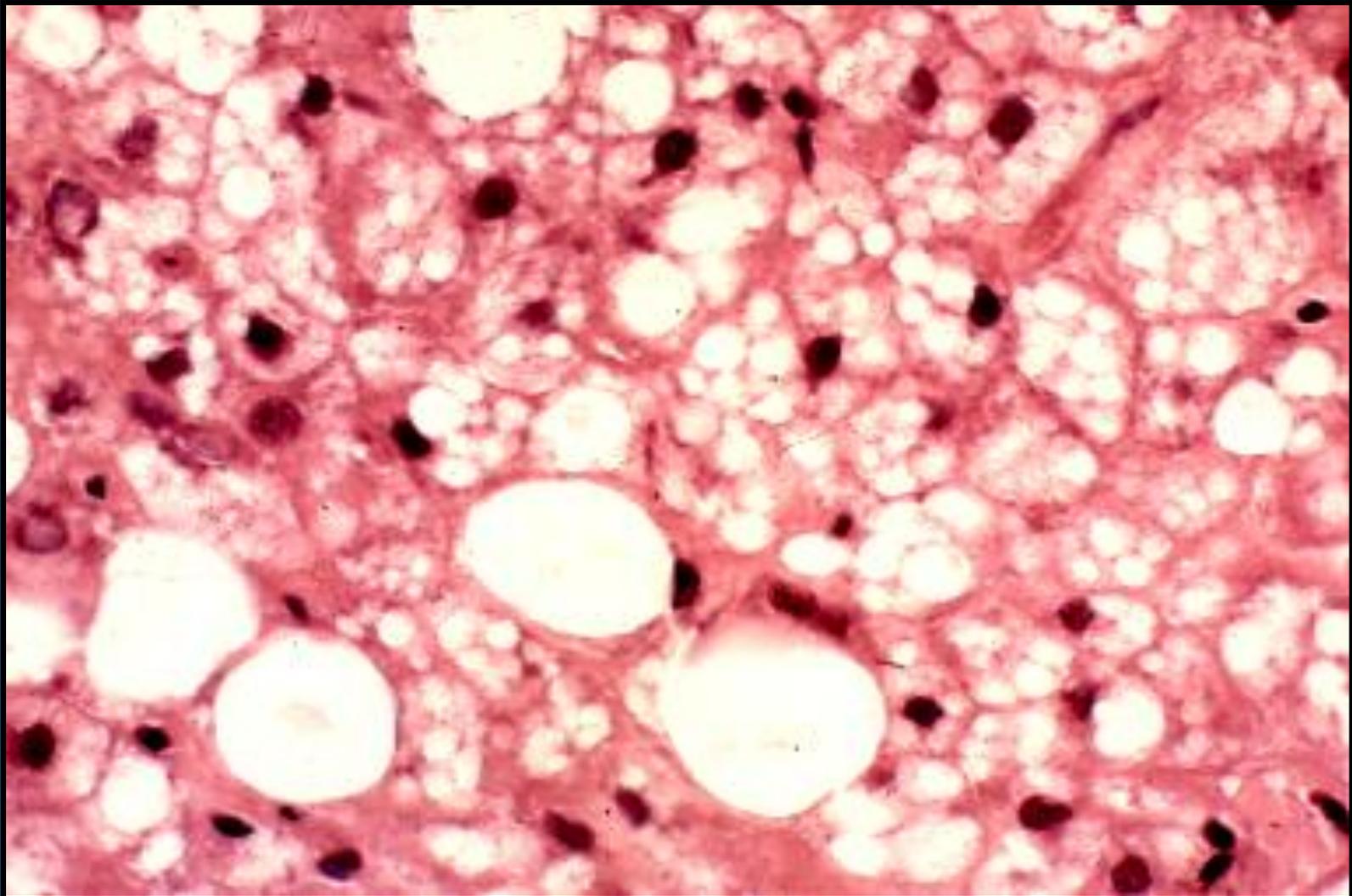
- Borde irregular de los espacios porta
- Va desde focos aislados a severa (>50% de la circunferencia del espacio porta).



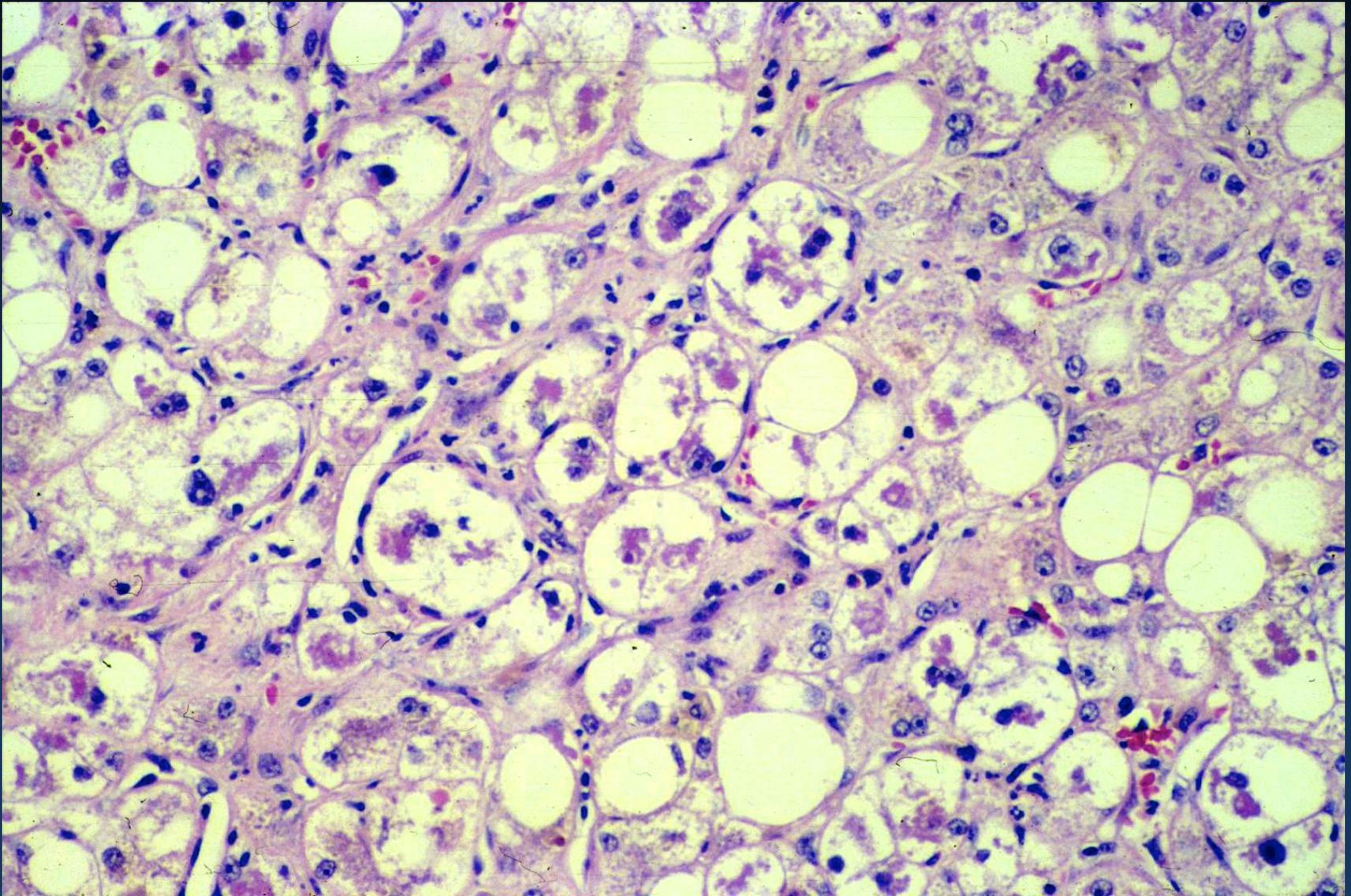
Esteatosis Macrovesicular



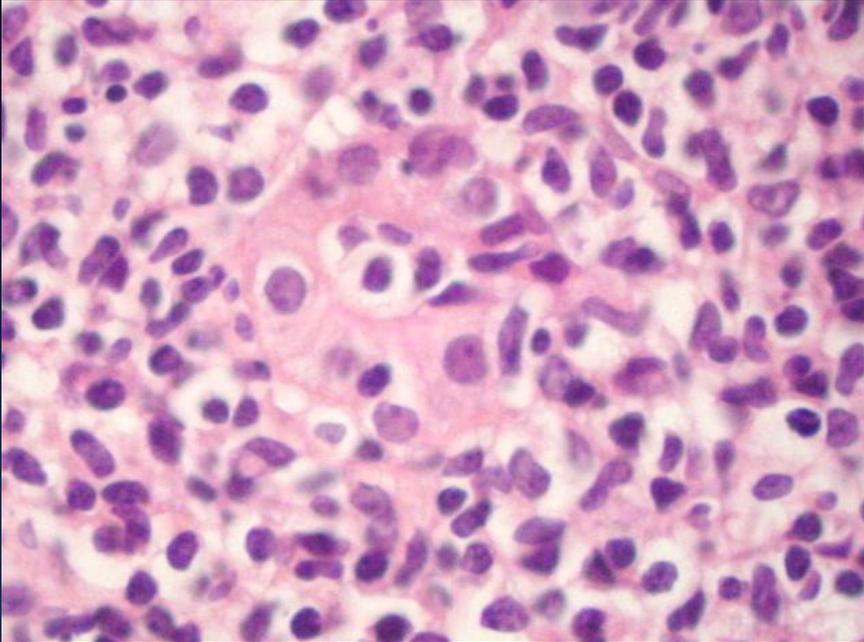
Esteatosis microvesicular



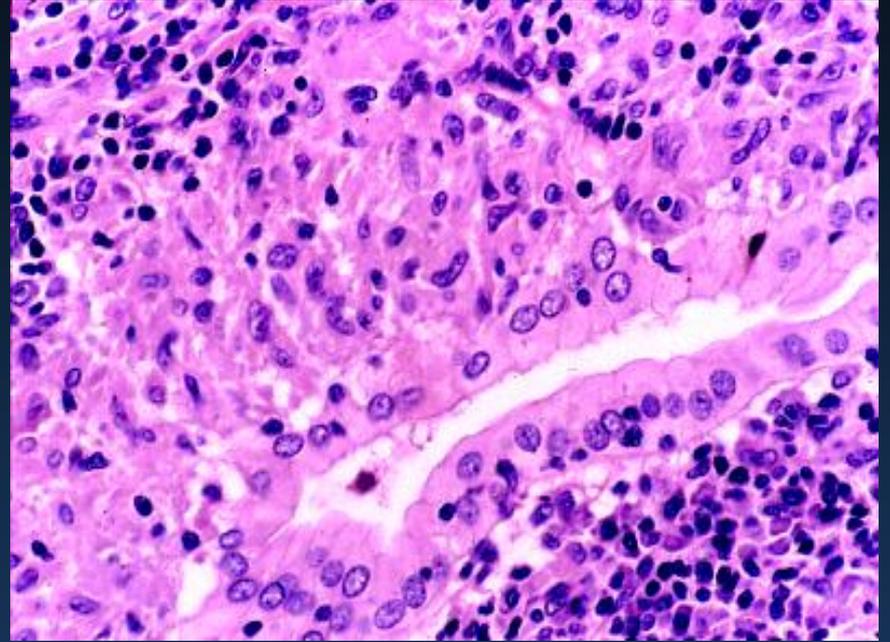
Cuerpos de Mallory-Denk



Colangitis

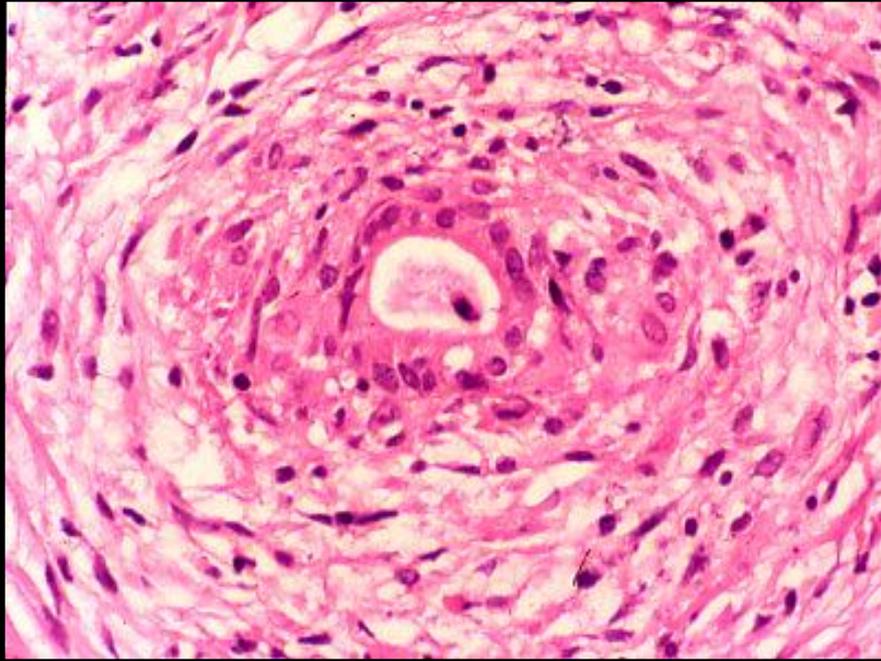


LINFOCÍTICA

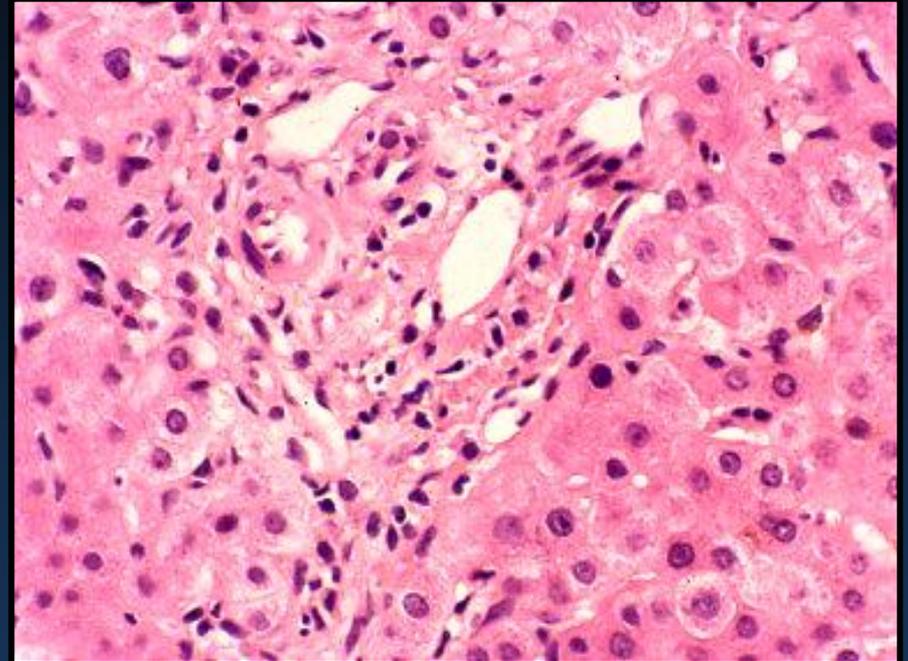


GRANULOMATOSA

Colangitis

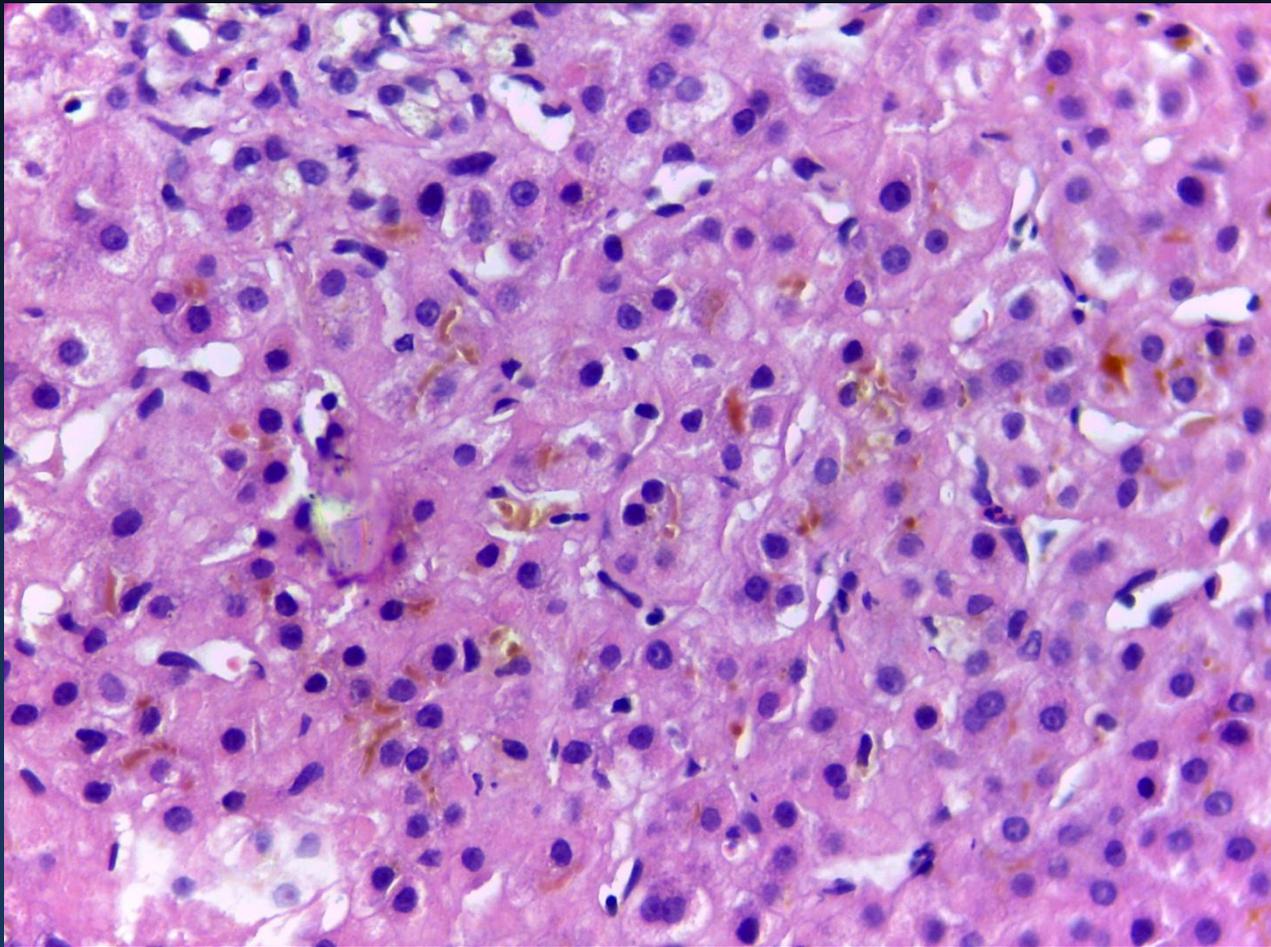


FIBROSANTE

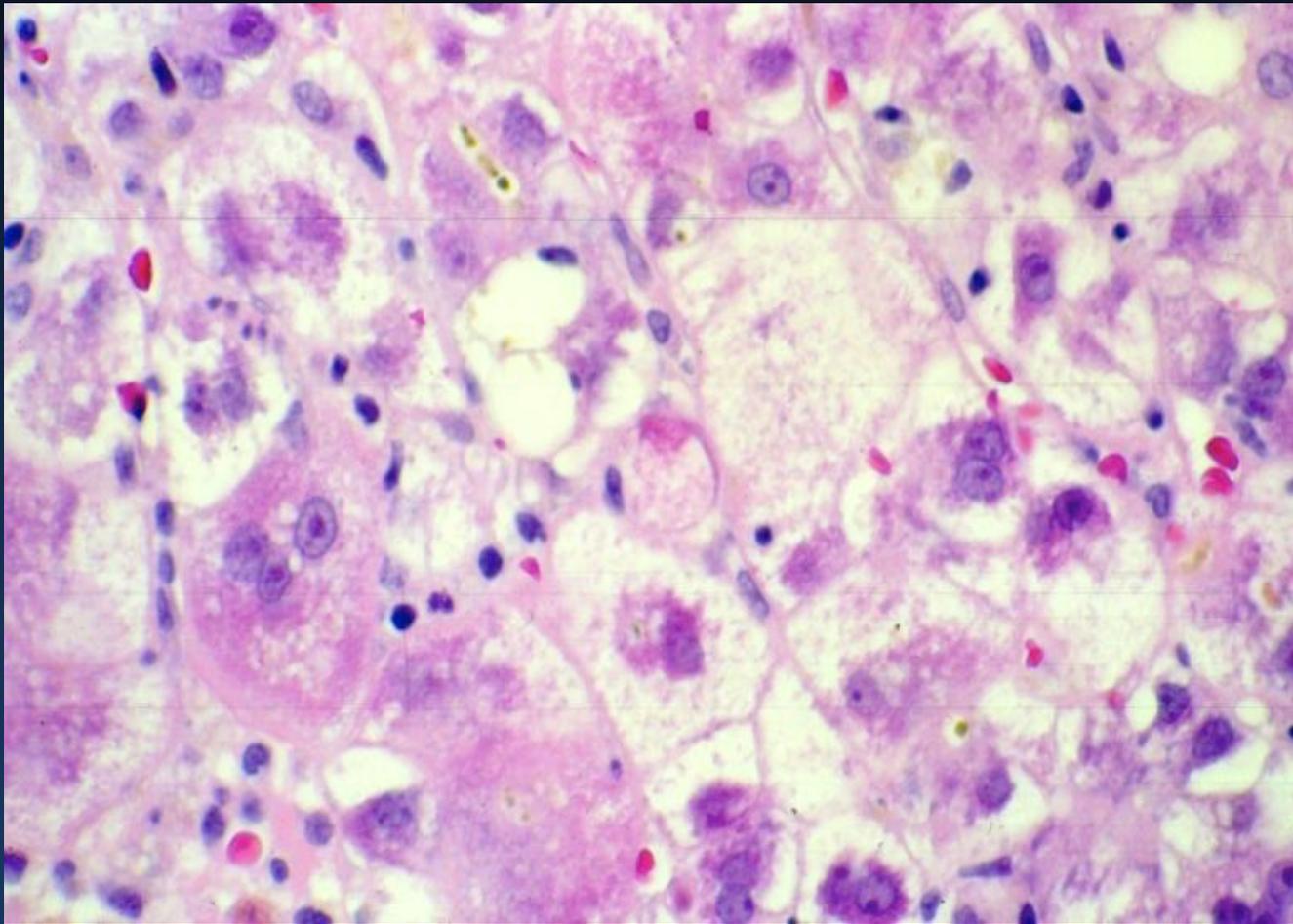


DUCTOPENIA

Colestasia - Aguda

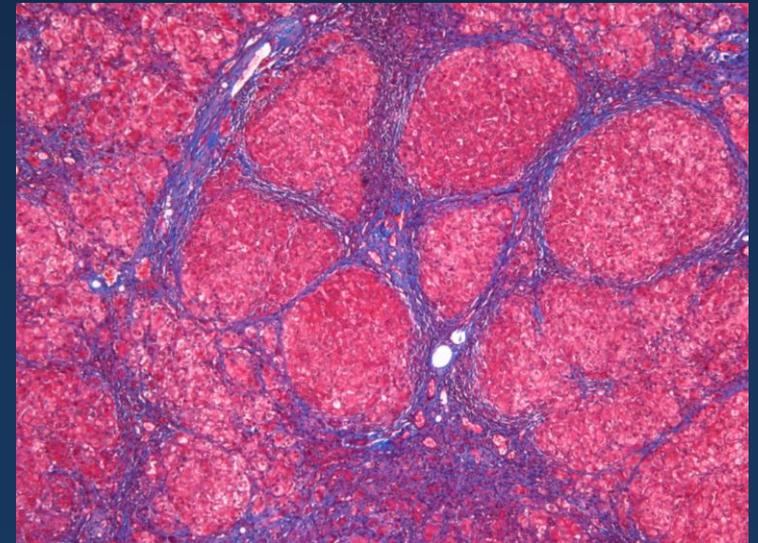
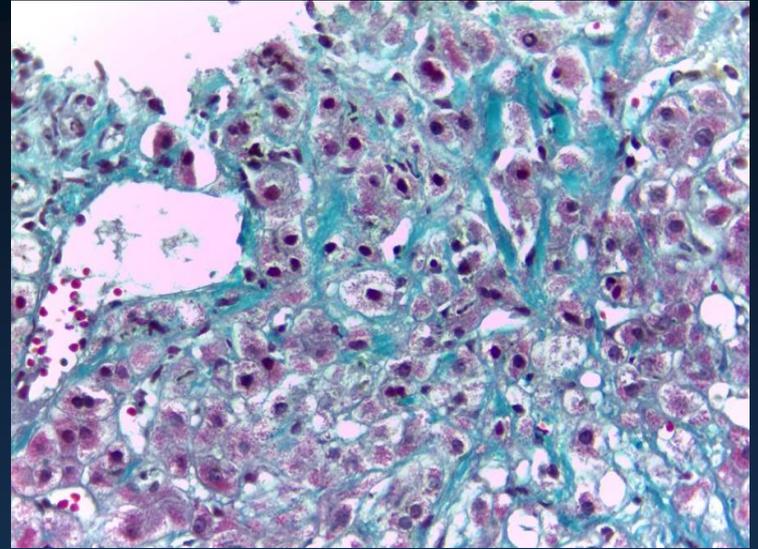


Colestasia – crónica



Fibrosis

- Respuesta a inflamación o toxicidad directa de algún agente.
- Irreversible...?
- Si la fibrosis progresa → subdivisión en nódulos de hepatocitos que proliferan rodeados por tejido cicatrizal → CIRROSIS

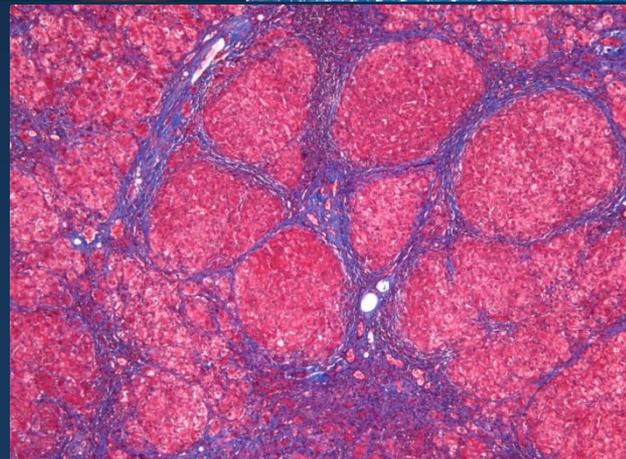


Cirrhosis

Macronodular
> 3mm



Micronodular
≤ 3mm



Características Patológicas de la Enfermedad Hepática

GRADACION Y ESTADIAJE

Hepatitis Crónica: Gradación y Estadiaje

Gradación:

Grado de Inflamación

(focos de necrosis parenquimatosa & hepatitis de interfase)

Estadio:

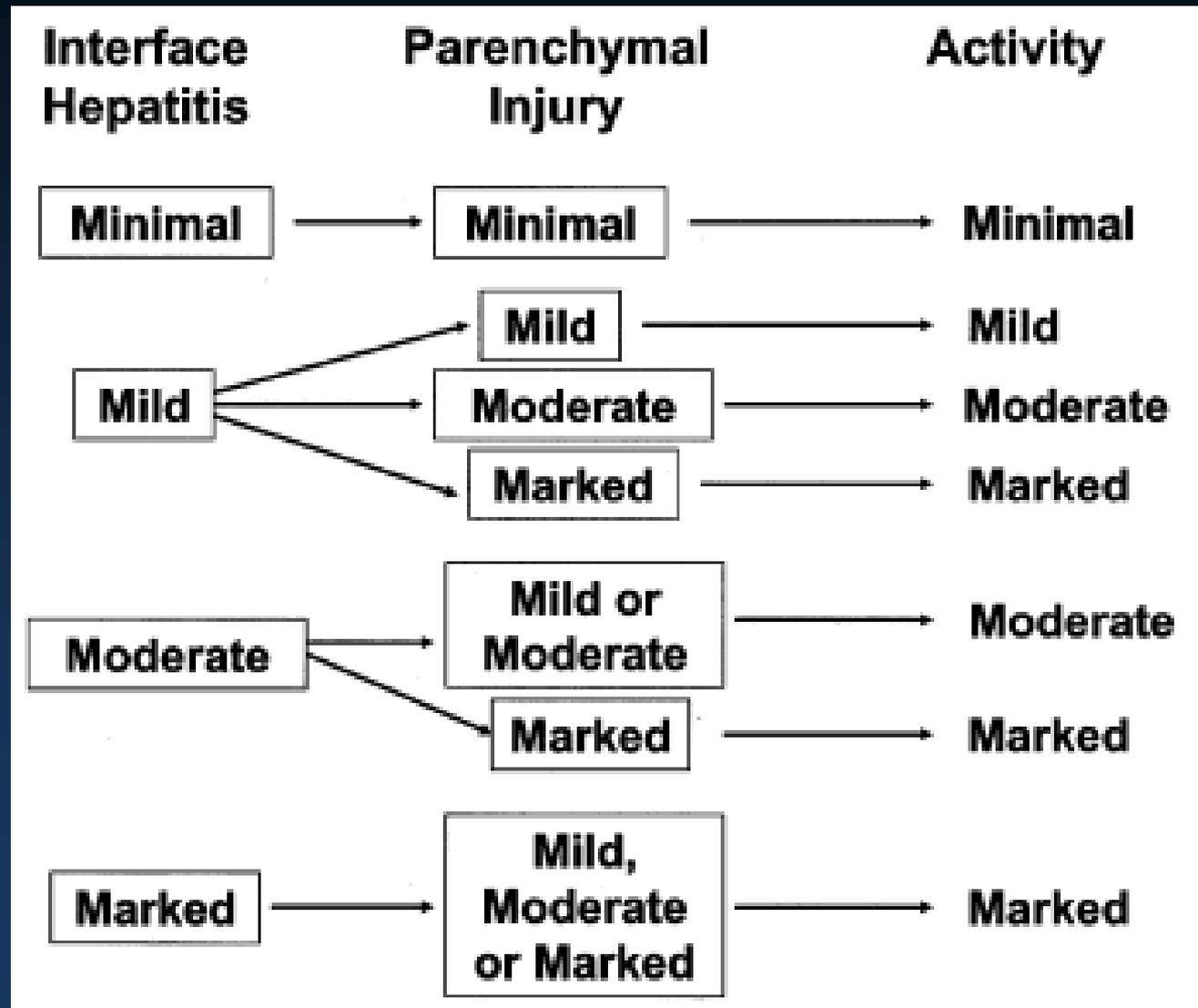
Grado de Fibrosis

(Fibrosis portal, septos fibrosos, fibrosis en puente, cirrosis)

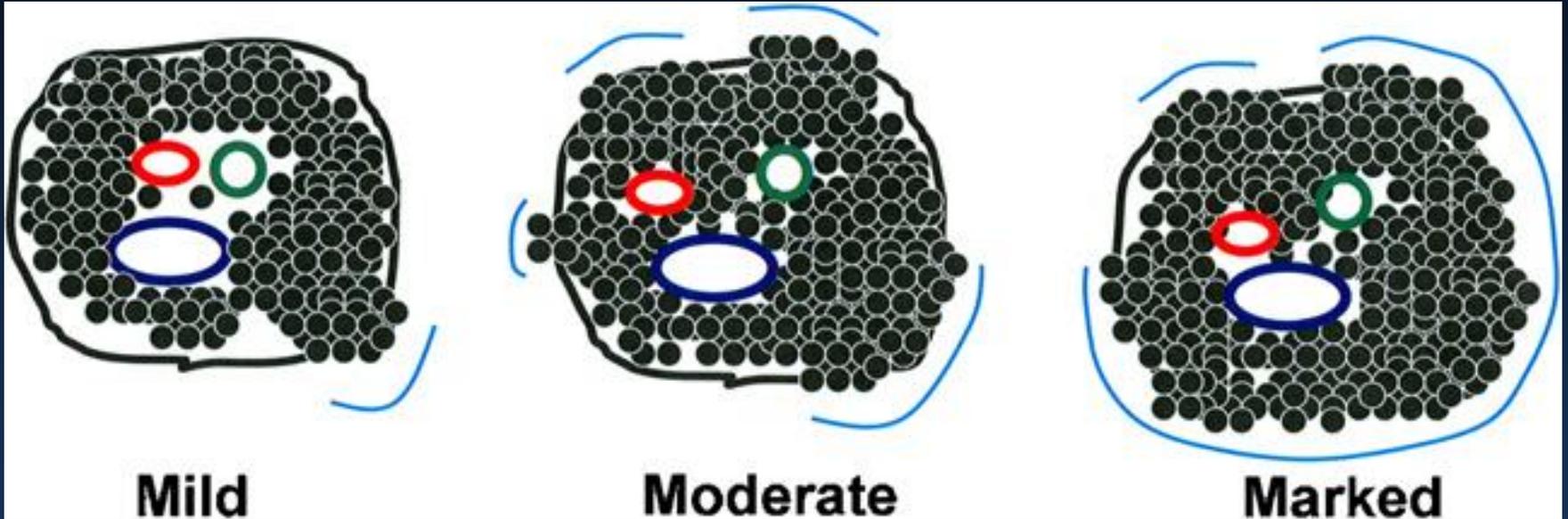
Hepatitis Crónica: Gradación y Estadiaje

- Varios sistemas de gradación y estadiaje:
 - Simples
 - Sheuer, Batts and Ludwig, Metavir, otros.
 - Preferibles para la práctica rutinaria y manejo de pacientes
 - Complejos
 - Preferibles para investigación
 - Análisis estadísticos
 - Clinical Trials

Batts and Ludwig: gradación

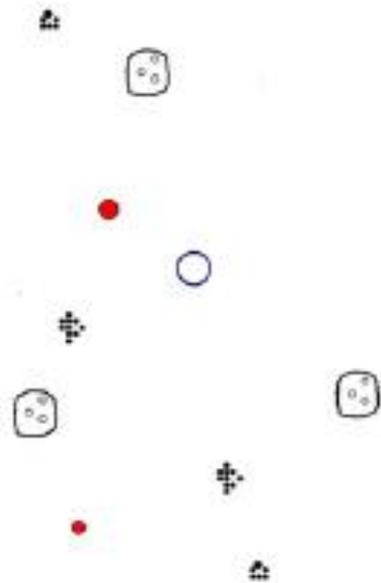


Batts and Ludwig Hepatitis de Interfase



Batts and Ludwig

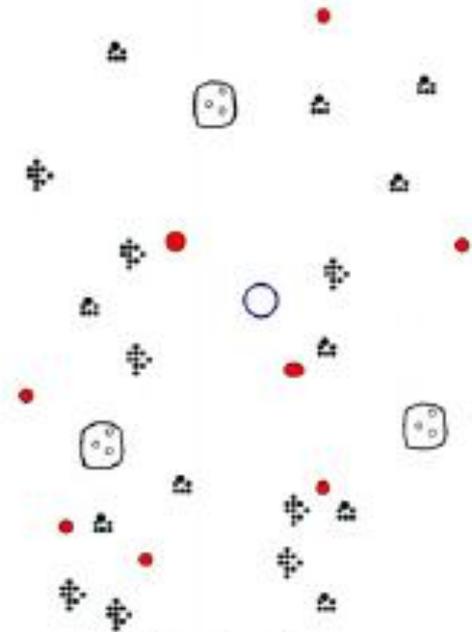
Actividad Lobulillar



Mild

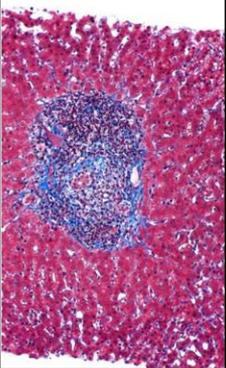
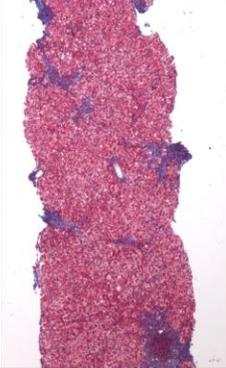
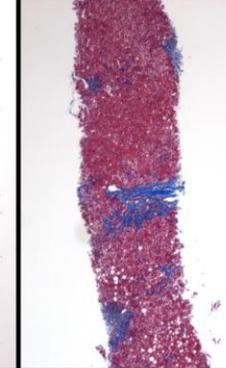
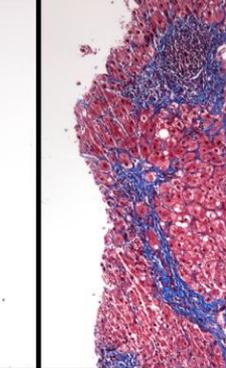
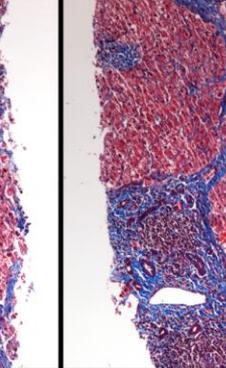
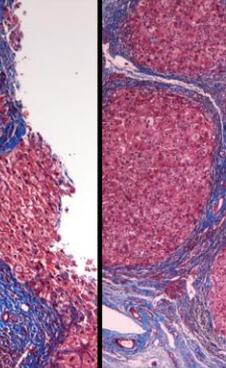


Moderate



Marked

Batts and Ludwig: estadiaje

Staging system						
Ishak	1	2	3	4	5	6
METAVIR	1	2	2	3	3	4
Scheuer	1	2	2	3	4	4
Batts & Ludwig	1	1	2	3	4	4

Falla Hepática

- Consecuencia más severa de la enfermedad hepática
- Puede resultar de:
 - Destrucción hepática repentina y masiva
 - Punto final del daño progresivo de una enfermedad hepática crónica
 - Se debe perder 80-90% de la capacidad funcional hepática
- Transplante hepático
 - Única esperanza de sobrevivir, de lo contrario 70-90% morirá sin él



PATOLOGÍA HEPÁTICA TUMORAL

Clasificación

- O.M.S.
- AFIP Atlas of Pathology

	Benign	Malignant
Hepatocellular tumours	Hepatocellular adenoma Focal nodular hyperplasia Dysplastic nodule	Hepatocellular carcinoma Fibrolamellar hepatocellular carcinoma Combined hepatocellular-cholangiocarcinoma Carcinosarcoma Hepatoblastoma
Biliary tumours	Von Meyenburg complex Bile duct cyst Ciliated foregut cyst Bile duct adenoma Biliary adenofibroma Microcystic adenoma Intraductal papillary neoplasm Mucinous cystic neoplasm	Cholangiocarcinoma Mucinous cystic neoplasm with associated carcinoma
Vascular tumours	Haemangioma Infantile haemangioma Lymphangioma	Angiosarcoma Epithelioid haemangioendothelioma
Other tumours	Angiomyolipoma Mesenchymal hamartoma Inflammatory pseudotumour	Primary lymphomas Embryonal (undifferentiated) sarcoma Germ cell tumours Other sarcomas and rare tumours

Clasificación

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Diagnóstico diferencial

- Edad
- Sexo
- Factores predisponentes
 - Enfermedad de base
 - Drogas
 - Químicos
 - Parásitos

	Benign	Malignant
Hepatocellular tumours	Hepatocellular adenoma Focal nodular hyperplasia Dysplastic nodule	Hepatocellular carcinoma Fibrolamellar hepatocellular carcinoma Combined hepatocellular-cholangiocarcinoma Carcinosarcoma Hepatoblastoma
Biliary tumours	Von Meyenburg complex Bile duct cyst Ciliated foregut cyst Bile duct adenoma Biliary adenofibroma Microcystic adenoma Intraductal papillary neoplasm Mucinous cystic neoplasm	Cholangiocarcinoma Mucinous cystic neoplasm with associated carcinoma
Vascular tumours	Haemangioma Infantile haemangioma Lymphangioma	Angiosarcoma Epithelioid haemangioendothelioma
Other tumours	Angiomyolipoma Mesenchymal hamartoma Inflammatory pseudotumour	Primary lymphomas Embryonal (undifferentiated) sarcoma Germ cell tumours Other sarcomas and rare tumours

Clasificación por características clínicas mayores

Tumours of infancy and young children	Infantile haemangioma
	Mesenchymal hamartoma
	Hepatoblastoma
Tumours of older children and young adults	Fibrolamellar hepatocellular carcinoma
	Embryonal sarcoma
Tumours much more frequent in men	Hepatocellular carcinoma
Tumours much more frequent in women	Hepatocellular adenoma
	Mucinous cystic neoplasm
Tumours associated with chronic liver disease and cirrhosis	Hepatocellular carcinoma
Tumours associated with chemical or drug exposure	Hepatocellular adenoma
	Hepatocellular carcinoma
	Angiosarcoma
Tumours associated with parasitic infections and inflammatory diseases of the biliary tract	Cholangiocarcinoma
Tumours associated with congenital anomalies and metabolic diseases	Hepatocellular carcinoma
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Factores de riesgo

Neoplastic condition	Risk factors
Adenoma	Oral contraceptive exposure
	Glycogen storage disease type 1a (Von Gierke disease)
Hepatocellular carcinoma	Viral hepatitis
	Hepatitis B infection
	Hepatitis C infection
	Cirrhosis from other causes
	Alcoholic liver disease
	Hereditary haemochromatosis
	Hereditary tyrosinaemia
	α 1-antitrypsin storage disorder
	Wilson disease (rare)
	Primary biliary cirrhosis (rare)
	Inherited disorders without obligate cirrhosis
	Glycogen storage disease type 1a (Von Gierke disease)
Hepatoblastoma	Familial adenomatous polyposis (FAP)
Cholangiocarcinoma	Primary sclerosing cholangitis
	Fluke infection of the biliary tract
Angiosarcoma	Toxin exposure ^a
	Vinyl chloride
	Arsenic

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Adenoma Hepatocelular (HCA)

- Definición
 - Tumor benigno.
 - Hígado no-cirrótico que se asemeja mucho a hepatocitos normales.
 - Múltiple (>10) → “adenomatosis hepática”

Adenoma Hepatocelular (HCA)

- Etiología y clínica
 - Mujeres (15-45 años).
 - Anticonceptivos orales (ACO) esteroidales y esteroidea anabólicos/androgénicos.
 - Incidencia 3-4/100.000 usuarios de ACO vs 1/1 million ACO (-).
 - Mecanismo exacto: ????
 - 33-56% asintomáticos.
 - 18-21% dolor abdominal agudo por hemorragia intratumoral o la cavidad peritoneal (potencialmente mortal)
 - Componente hepatocelular: monoclonal

Adenoma Hepatocelular (HCA)

- Tratamiento
 - Excisión quirúrgica
 - Riesgo de ruptura y sangrado
 - Riesgo de malignización
 - Manejo conservador vs transplante hepático
 - Tumores irresecables
 - Adenomatosis

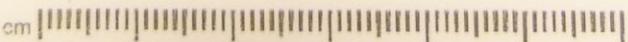
Adenoma Hepatocelular (HCA)

- Macroscopía:
 - Tumores hepáticos solitarios protruyentes o pedunculados.
 - Tamaño: 5 – 15 cm → 30 cm
 - Mejor tecnologías imagenológicas → < 5 cm
 - Usualmente no encapsulados
 - Bien delimitados del resto del hígado.
 - Color: amarillo o café claro.
 - Áreas verdosas de producción de bilis así como áreas de necrosis y hemorragia.

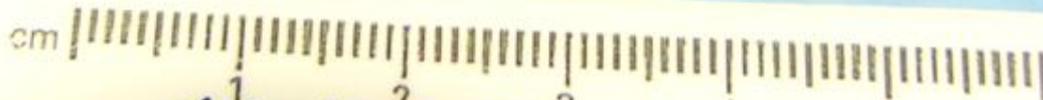


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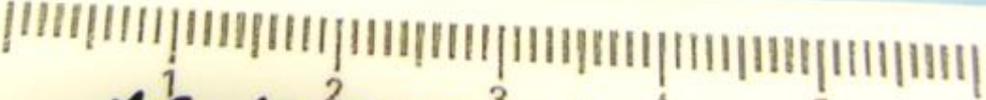
Adenoma Hepatocelular (HCA)

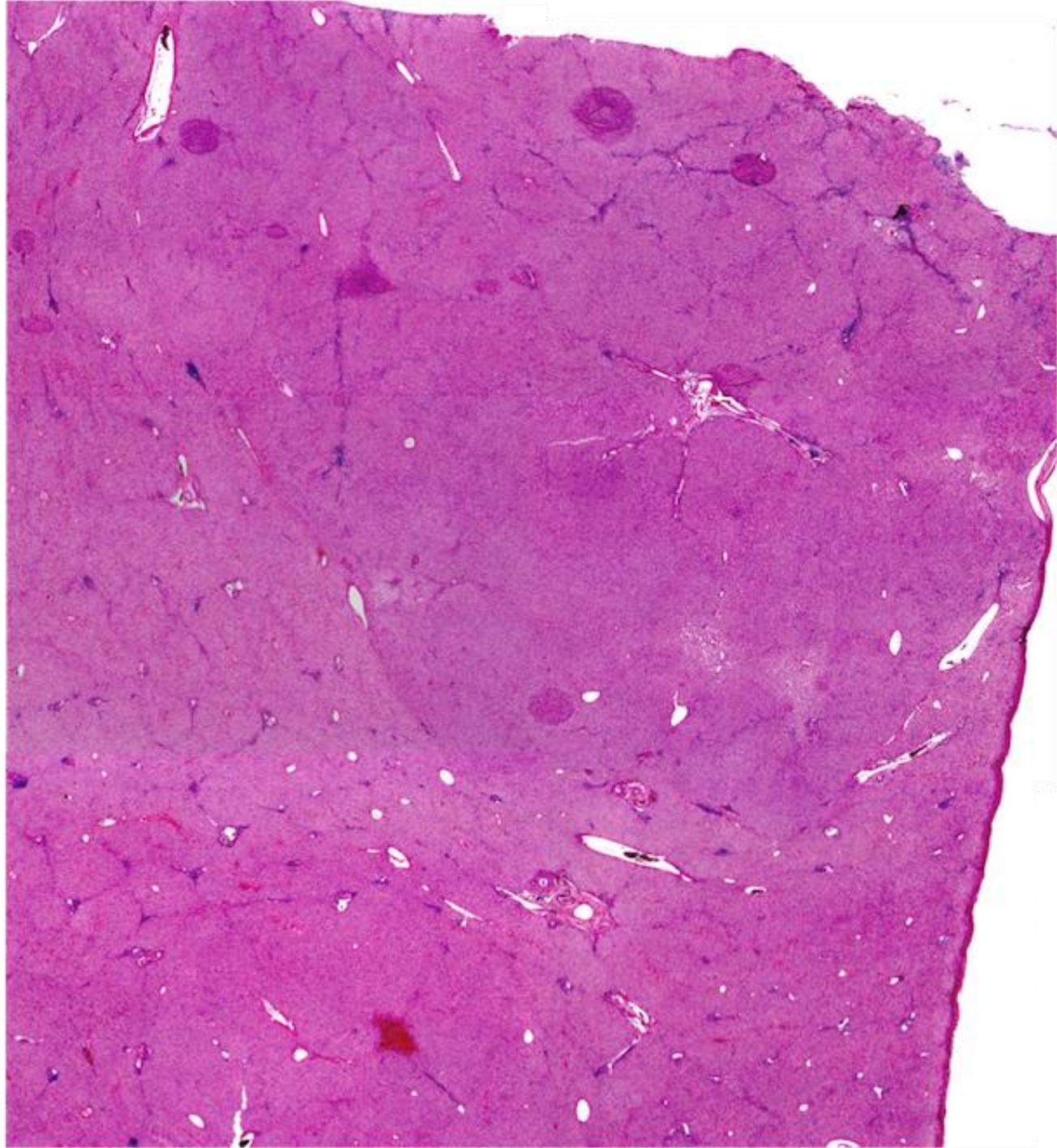
- Microscopía:
 - Hepatocitos benignos → láminas o cordones sin arquitectura acinar → ductos biliares ausentes.
 - Más grandes y pálidos → glícogeno o grasa → ~se puede confundir con enfermedad por hígado graso.
 - Núcleos uniformes y relación núcleo/citoplasma es baja.
 - Sinusoides: comprimidos y ocasionalmente dilatados.

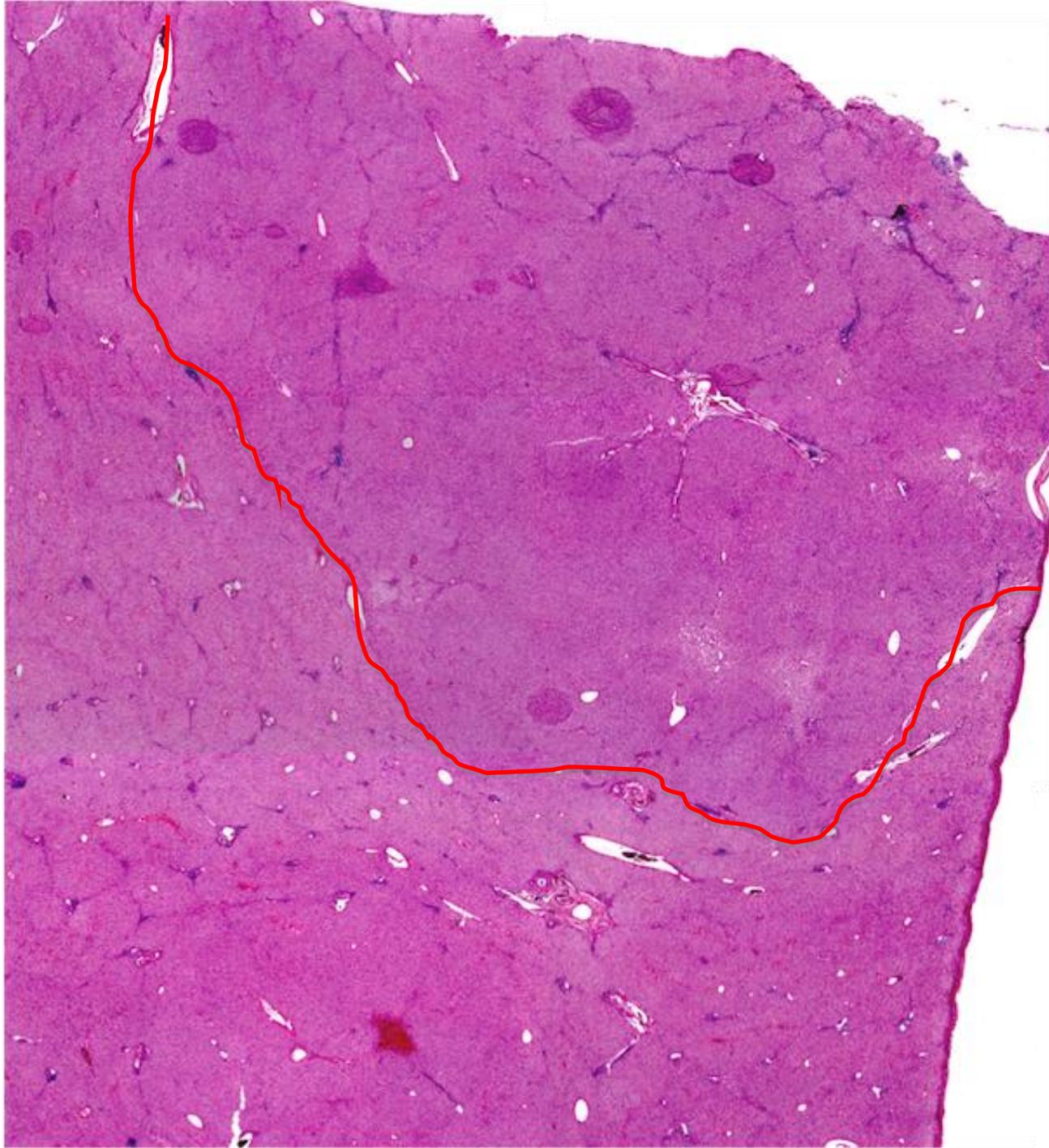
Adenoma Hepatocelular (HCA)

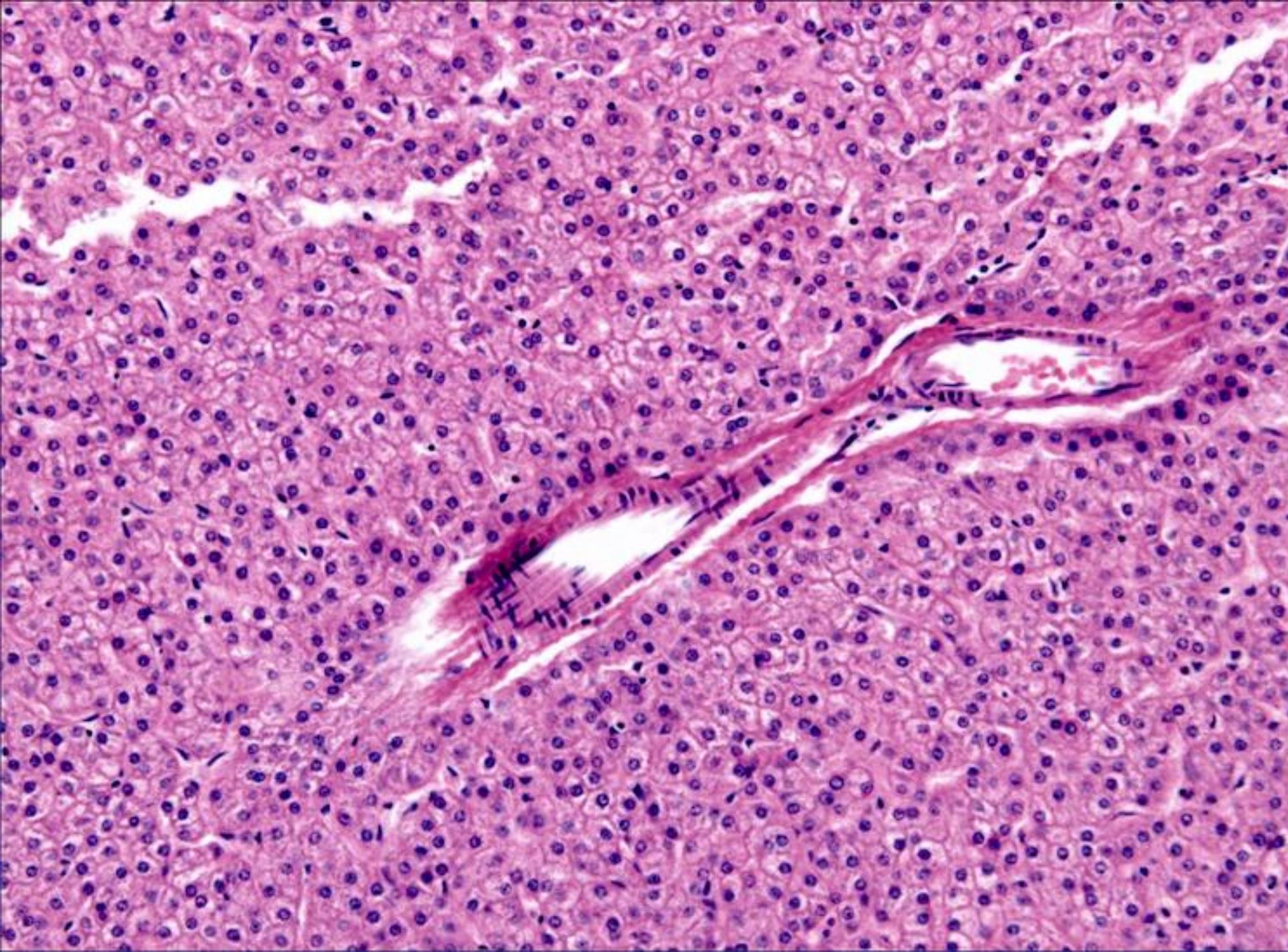
- Microscopía:
 - Sin cicatriz central o grandes arterias características de la Hiperplasia Nodular Focal.
 - Hemorragia e infartos (recientes o antiguos)



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Adenoma Hepatocelular (HCA)

- Tipos:
 - *HNF1 α* mutations
 - Telangiectatic or inflammatory
 - *β -catenin* activating mutations
 - No known mutations or special histologic features (NOS)

Hiperplasia Nodular Focal (FNH)

- Definición
 - Malformación de tipo tumoral o pseudotumoral.
 - Nódulos hiperplásticos de hepatocitos separados por septos fibrosos.
 - Cicatriz central estrellada.
 - Usualmente en hígados sanos.

Hiperplasia Nodular Focal (FNH)

- Clínica
 - Ambos sexos, todas las edades → mujeres adultas
 - Detección incidental → cirugía, imágenes.
 - Ocasionalmente: masa palpable.
 - Patogenia: flujo sanguíneo alterado → secuencia exacta???
 - Componente hepatocelular → policlonal (HCA es monoclonal)

Hiperplasia Nodular Focal Patología

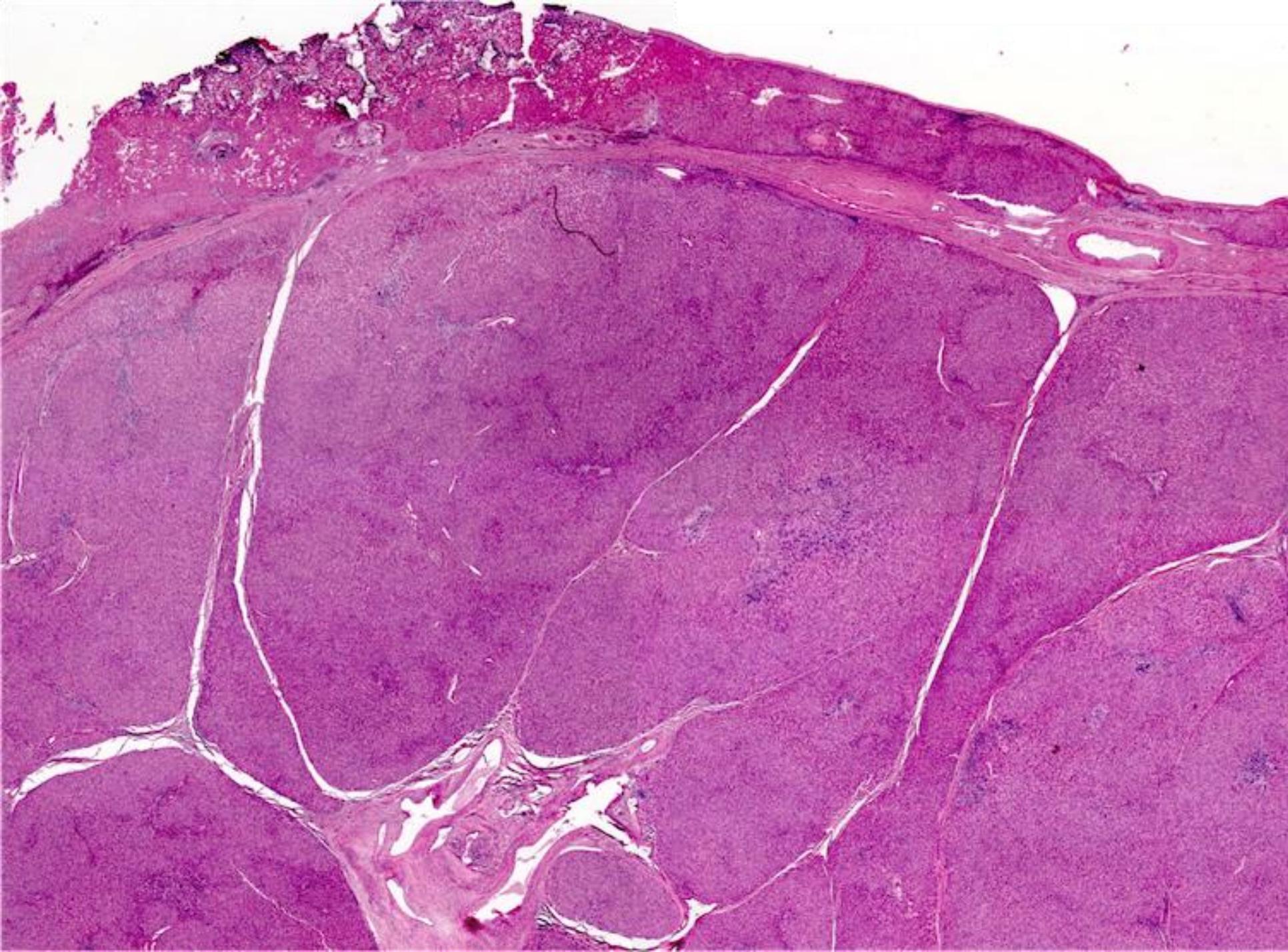
- Macroscopía
 - Bien delimitado, no-encapsulado
 - >85% son < 5 cm
 - Color más claro que el hígado.
 - Superficie de corte → nódulos más pequeños divididos por septos fibrosos → cicatriz estrellada central o excéntrica.

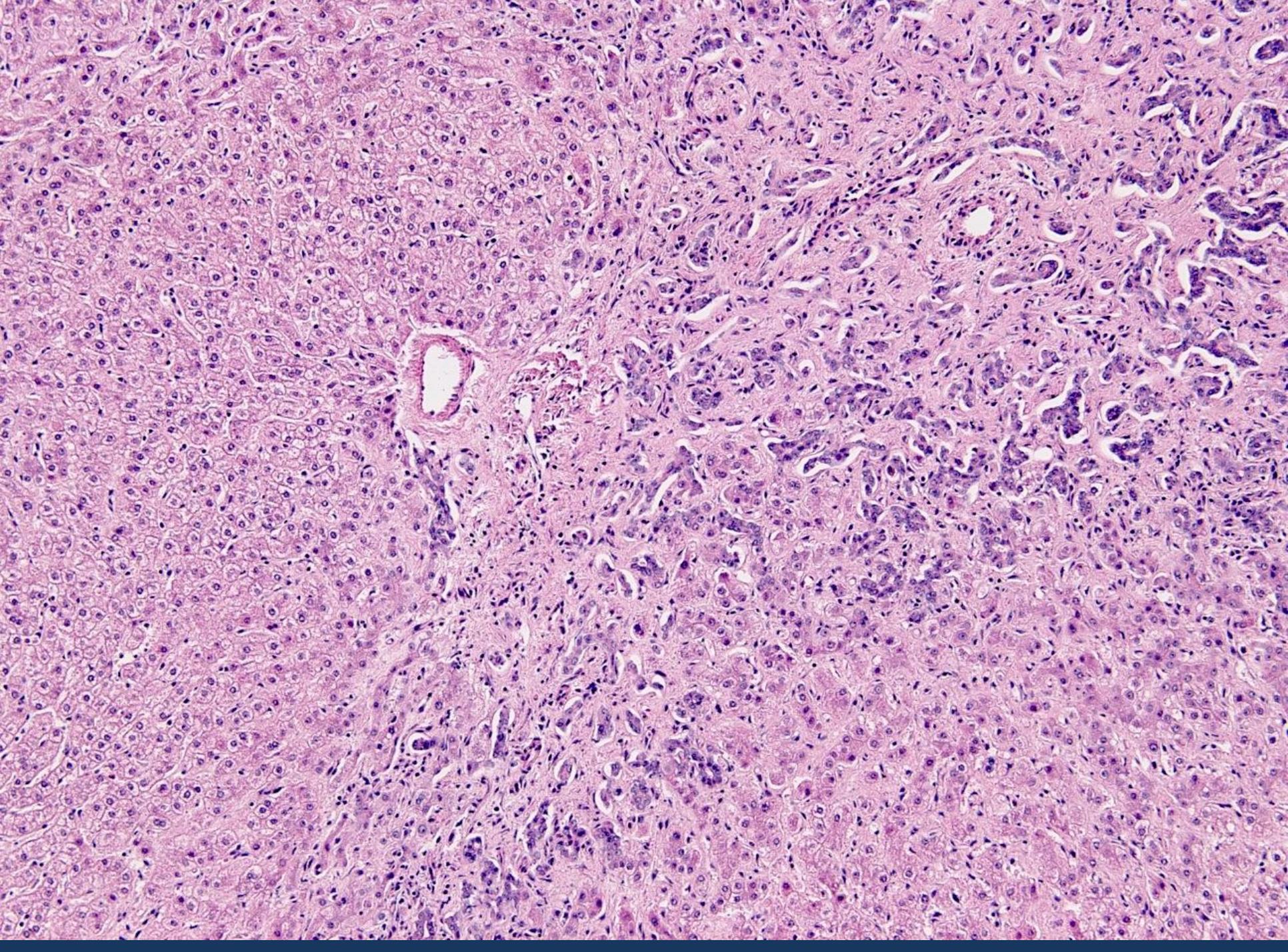


Hiperplasia Nodular Focal

Patología

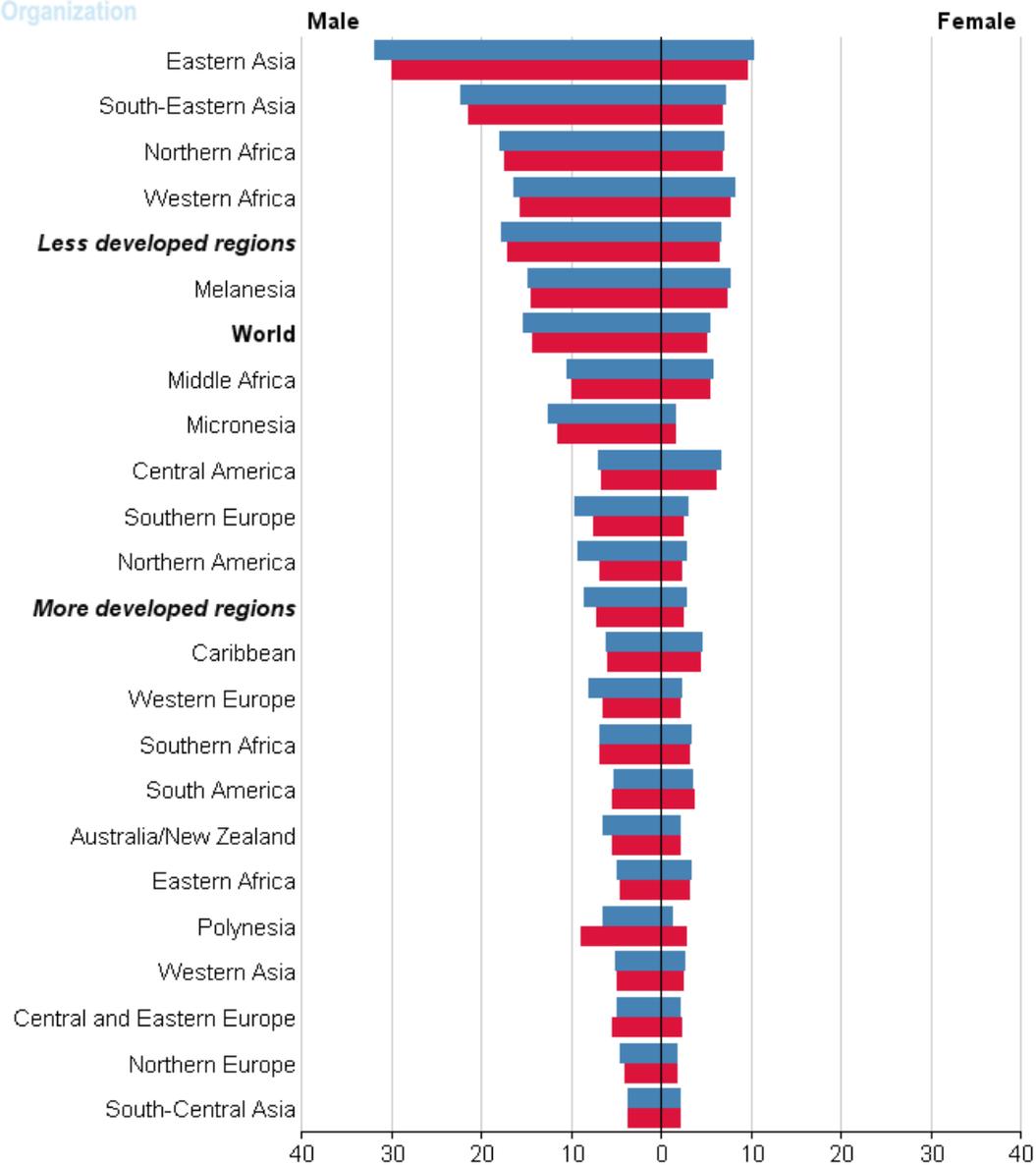
- Microscópicamente:
 - Septos fibrosos → células inflamatorias y conductillos pero no ductos biliares.
 - Vasos anormales → Especialmente arterias con engrosamiento excéntrico.
 - Hepatocitos tumorales → levemente más claros y pálidos.

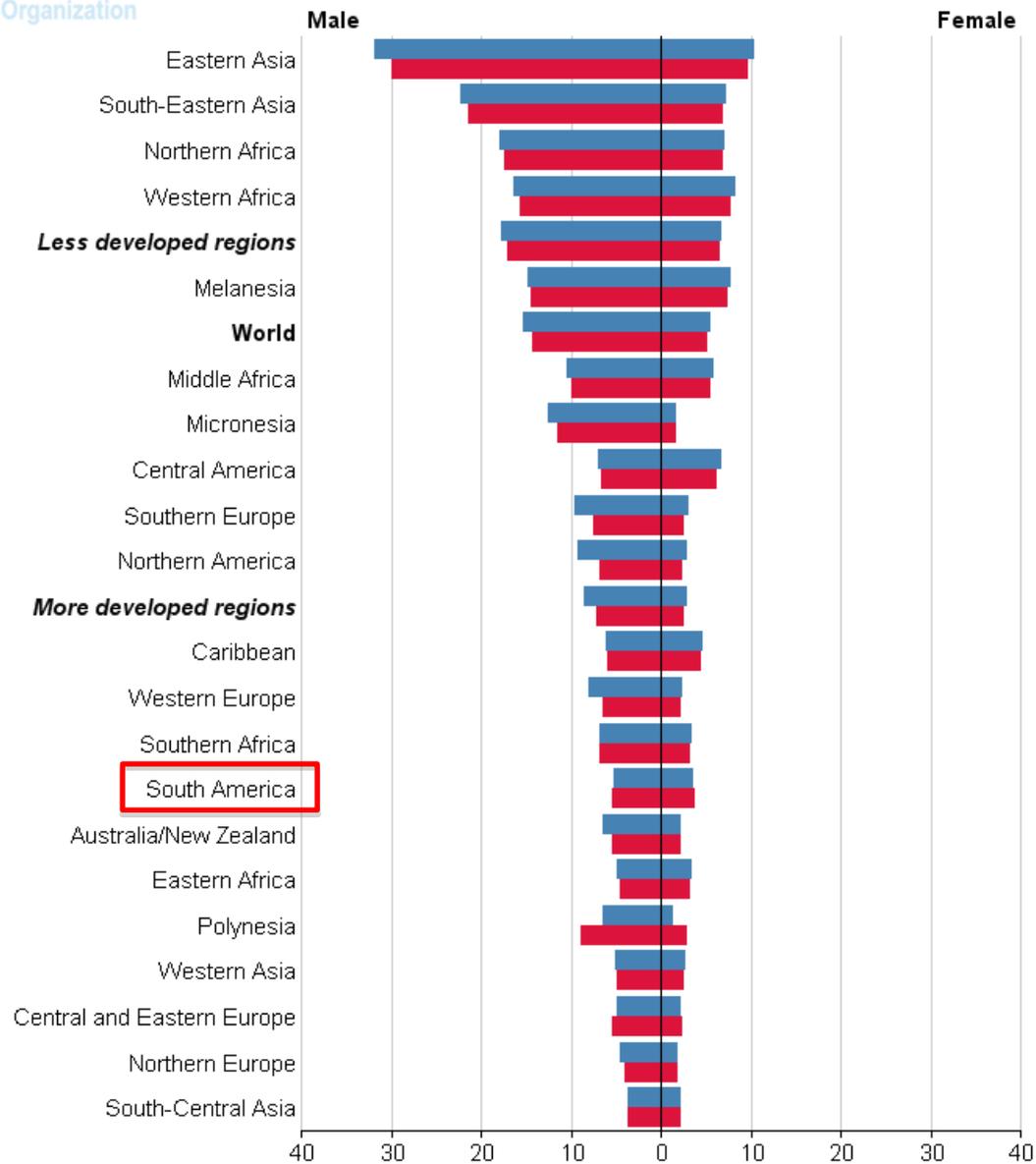




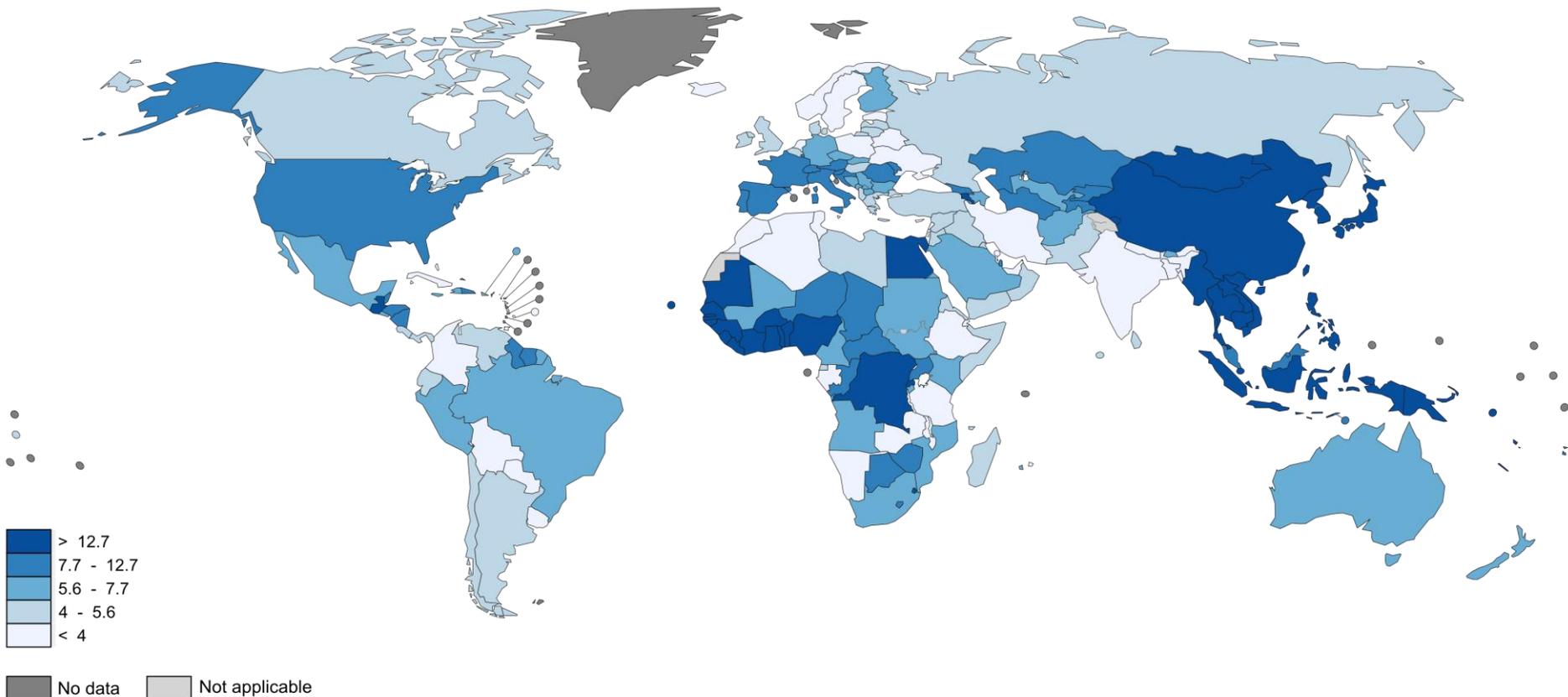
Carcinoma Hepatocelular (HCC)

- Tumor maligno primario más común en adultos.
- Enfermedad hepática de base → cirrosis → HCC
 - Hepatitis virales (HBV, HCV) → 70 - 80% HCC
 - Esteatohepatitis:
 - Alcohólica.
 - No-alcohólica (obesidad y diabetes).





Carcinoma Hepatocelular (HCC) Incidencia Mundial, 2012, hombres



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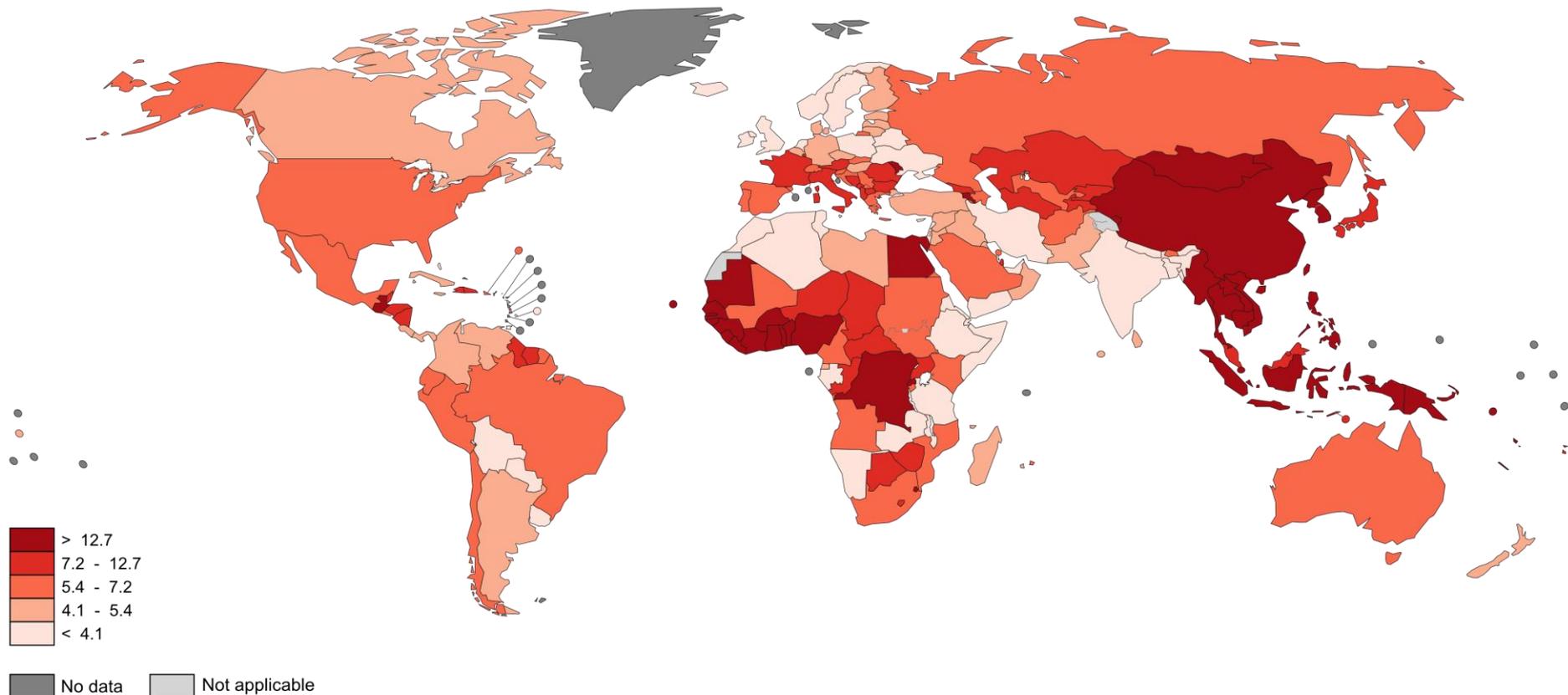
Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization



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Carcinoma Hepatocelular (HCC)

Mortalidad Mundial, 2012, hombres

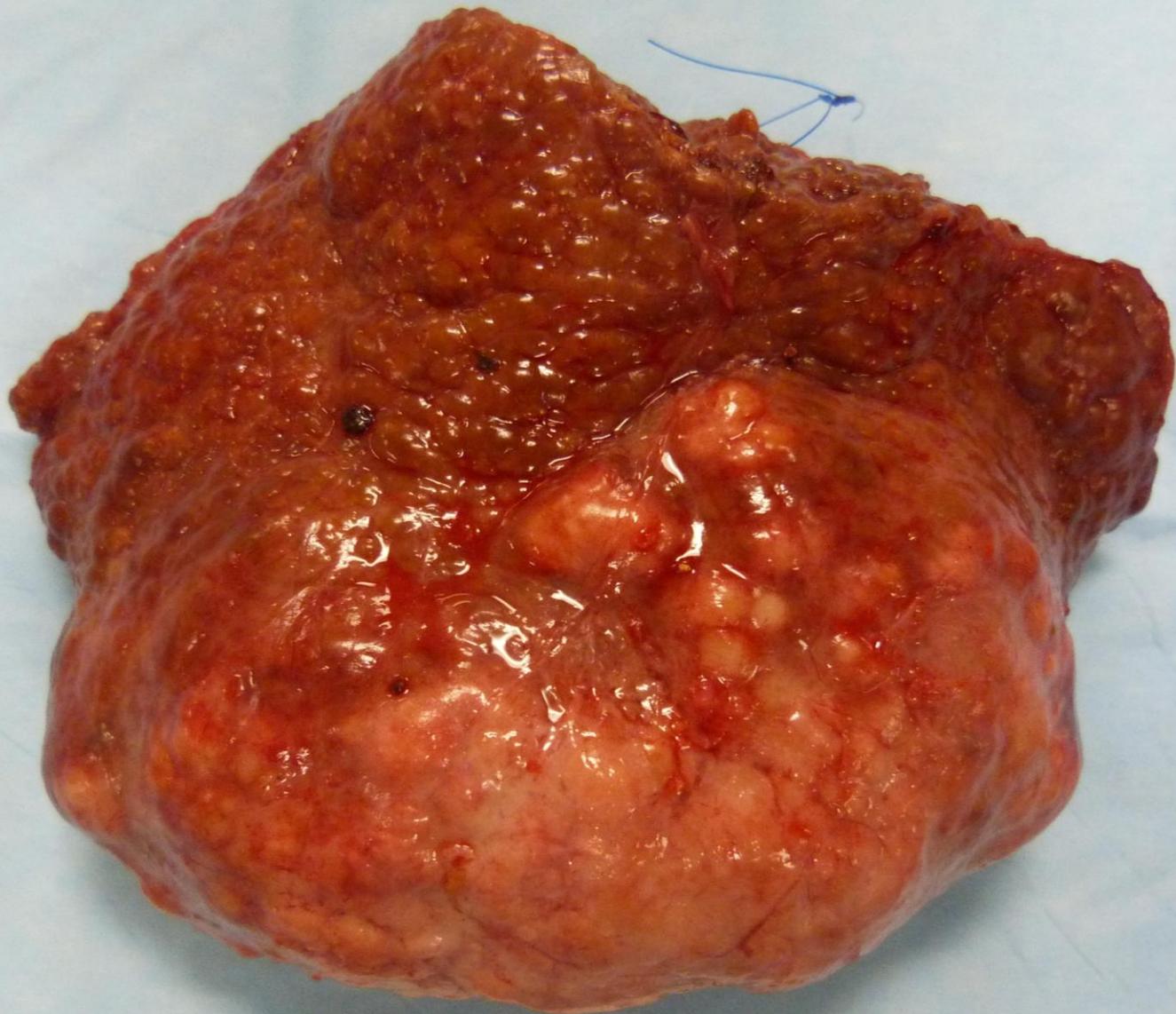


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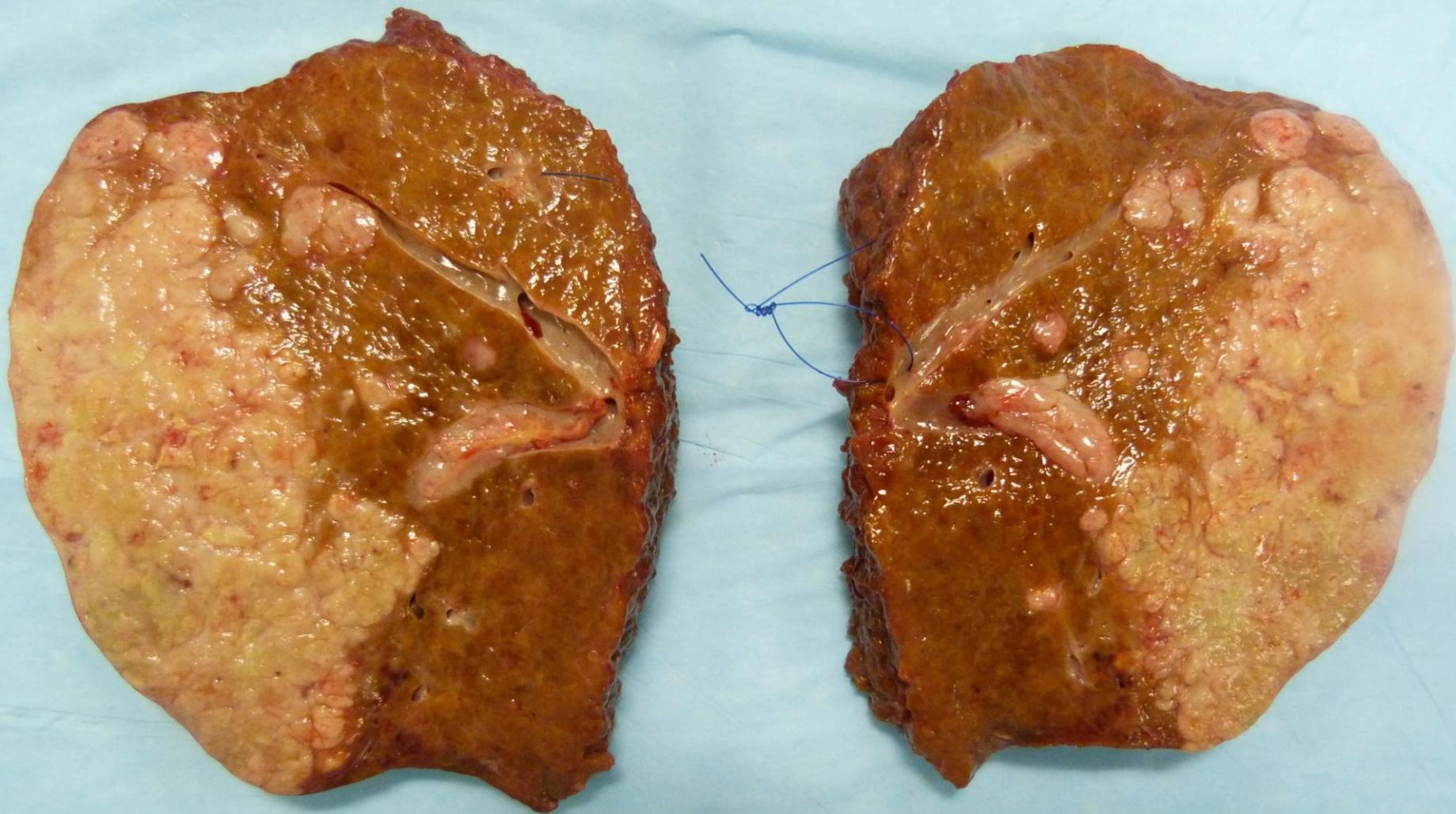
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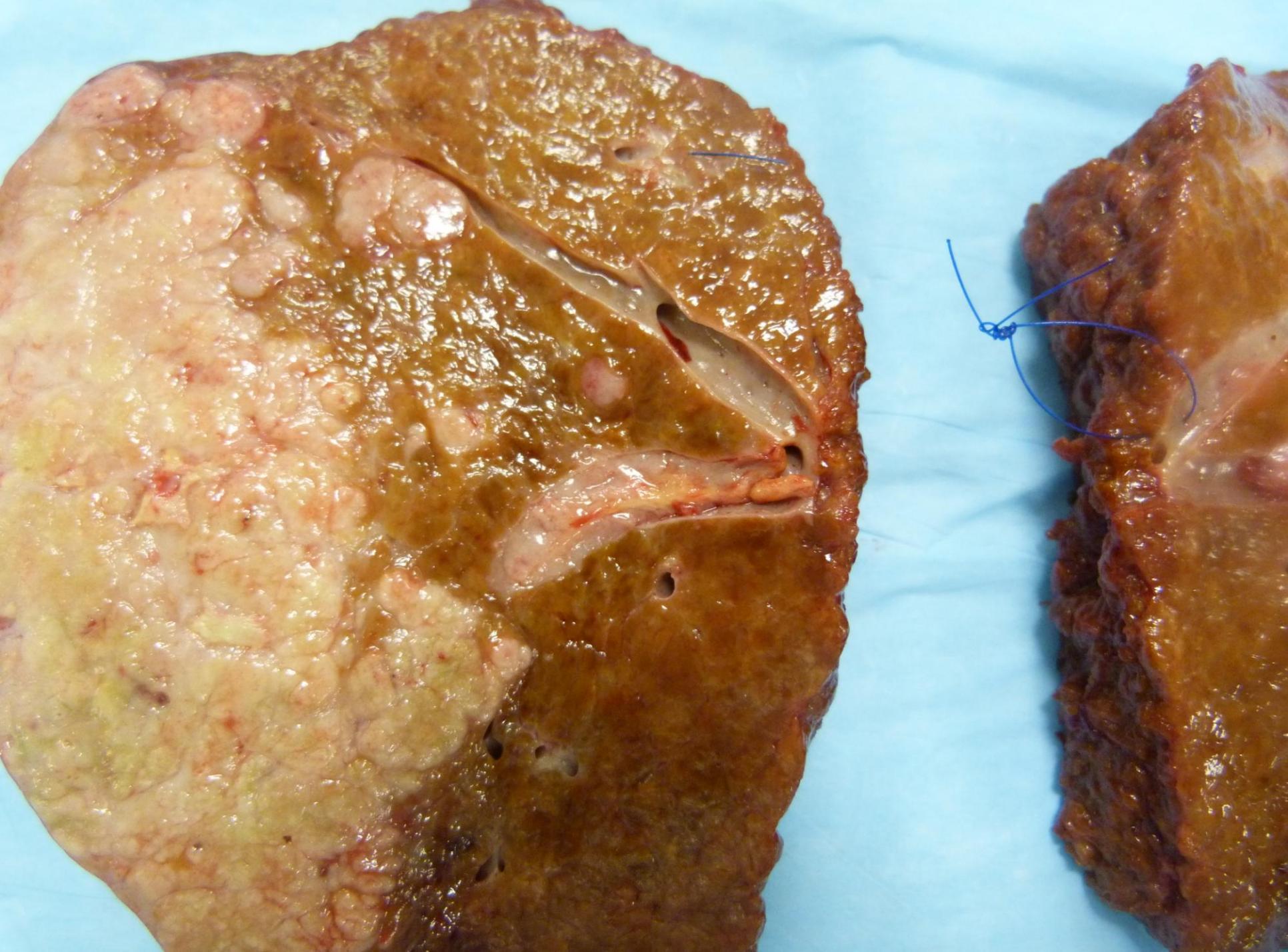
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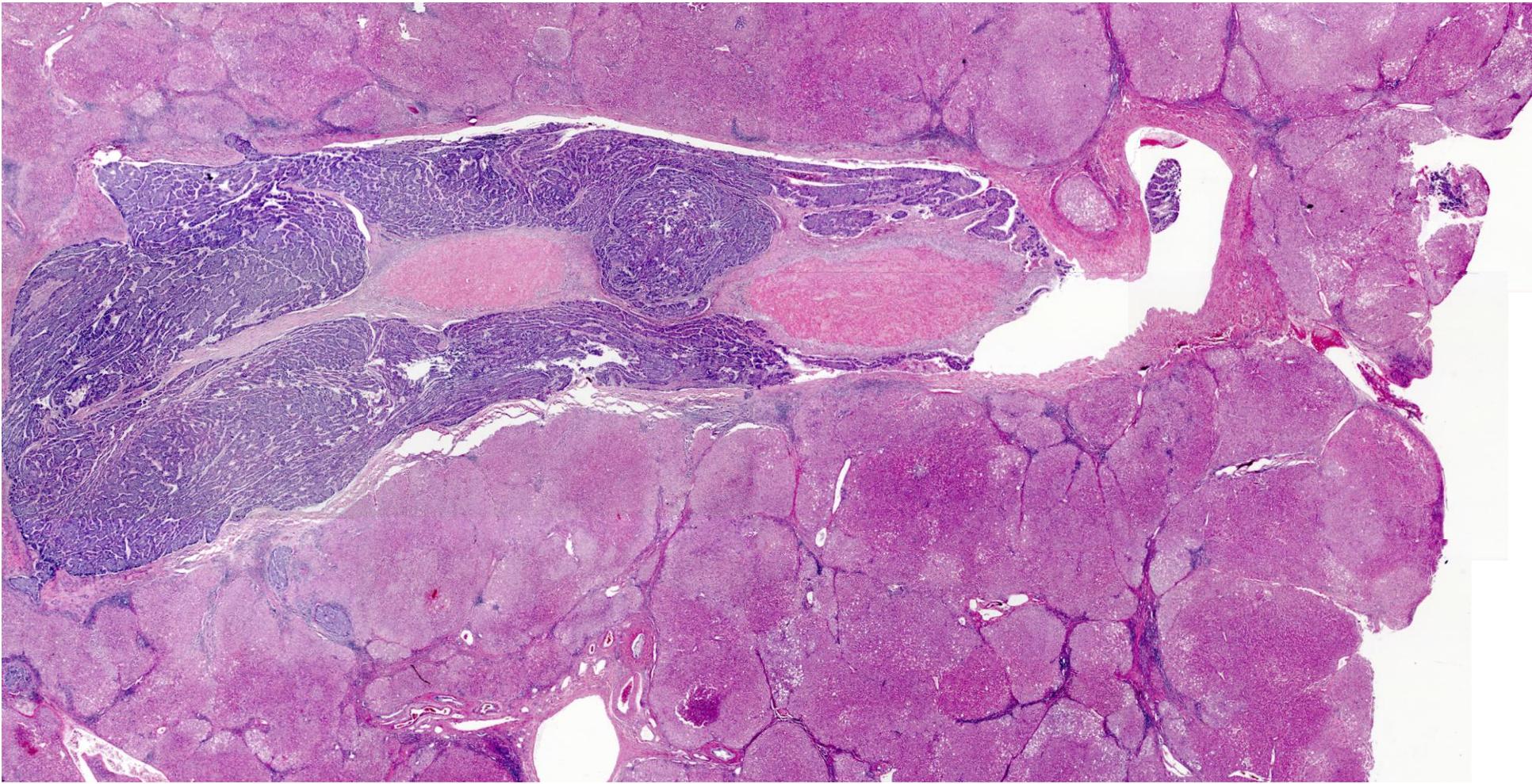


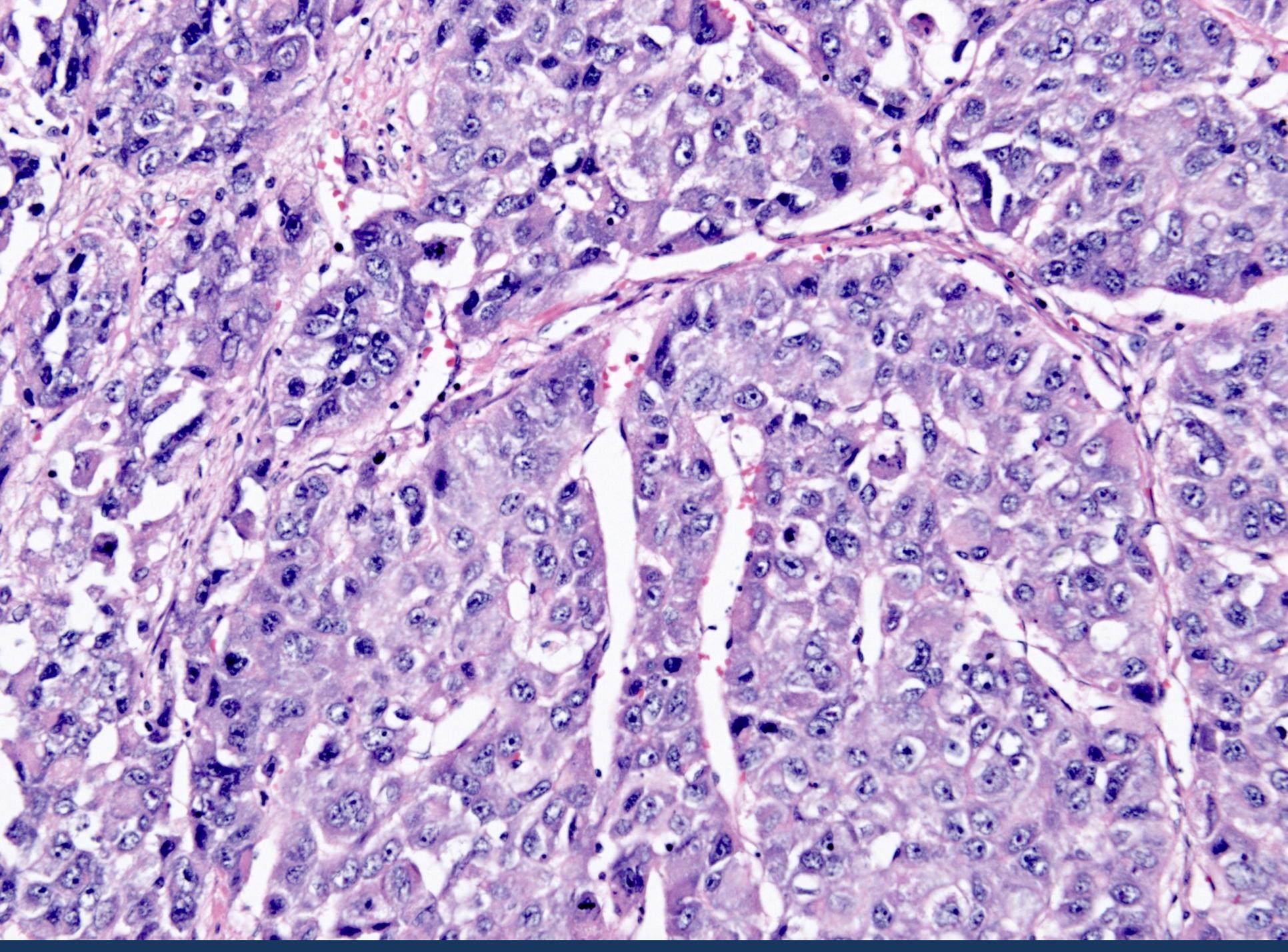
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BIOPSIA HEPÁTICA

Biopsia Hepática

- Establecer o confirmar el diagnóstico de una enfermedad hepática en particular.
- Determinar la severidad de la enfermedad.
 - Gradación
 - Estadiaje
- El diagnóstico SIEMPRE se debe realizar en conjunto con antecedentes clínicos.

Conclusiones

- Hay múltiples causas que pueden causar daño hepático
 - Infecciosas
 - Inmunes
 - Drogas
 - Metabólicas
 - Mecánicas
- Daño agudo y/o crónico
- Se manifiesta por lesiones elementales y fibrosis.

Conclusiones

- Tumores hepáticos.
 - Benignos:
 - Adenoma hepatocelular: proliferación clonal de hepatocitos
 - Hiperplasia nodular focal: proliferación policlonal → lesión pseudotumoral.
 - Malignos:
 - Carcinoma hepatocelular: tumor maligno primario más frecuente
 - Colangiocarcinoma.
- El diagnóstico diferencial depende de factores clínicos y factores predisponentes (ej.: enfermedad de base)

